Division of Research Resources Annual Report Fiscal Year 1983

(October 1, 1982 — September 30, 1983)

National Institutes of Health
Bethesda, MD 20205

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Report of the Director
Division of Research Resources

On September 15, 1982, the Director of the National Institutes of Health (NIH) announced the appointment of Dr. Betty H. Pickett as Director of the Division of Research Resources (DRR), effective October 1, 1982.

The Division's Fiscal Year 1983 operating budget was $217,411,000, allowing DRR to pay its commitments and full indirect costs. This budget provided over $74 million for continued support for 75 General Clinical Research Centers, $14 million for Biomedical Research Support Shared Instrument Grants, $1 million to begin an instrumentation initiative in the Minority Biomedical Research Support Program, and $2.5 million for additional high technology and engineering resources through the Biotechnology Resources Program. Six grants were made under provisions of the Small Business Innovation Development Act of 1982.

The new Director launched an intensive examination of the most pressing programmatic and organizational issues facing the DRR.

Among the most significant organizational changes were the establishment of the Office of Program Planning and Evaluation (OPPE) and the Office of Review (OR). Dr. W. Sue Badman was appointed Chief of the OPPE in September 1983. The OPPE coordinates new program developments, as well as analyses and evaluations of ongoing programs. Dr. Michael A. Oxman, Assistant DRR Director for Review, heads the Office of Review. The OR oversees the DRR's review policies and procedures, and conducts the first level review of applications to the Minority Biomedical Research Support Program.

Principal Division activities for Fiscal Year 1983 included the following administrative and programmatic actions:

- A contract was negotiated with the National Academy of Sciences to study current prospects and future needs in the field of biomedical research models and methods.

- Several new developments took place in the General Clinical Research Centers Program. An ad hoc committee met in May to consider updating the CLINFO system. Their recommendations include organizing an electronic mail network among the GCRCs, and adapting existing commercial software to CLINFO requirements. Follow-up activities continue in both these areas. The GCRC Program will implement the previously recommended concept of the small or "compact" center; this center will be a six-bed unit containing beds for research protocol patients only (A beds), and a limit of from 300 to 500 A patient days, with 500 outpatient visits. An award for such a center will be made in Fiscal Year 1984.

- Future plans for the Biotechnology Resources Program in nuclear magnetic resonance (NMR), high-voltage electron microscopy (HVEM), and

the PROPHET project were under detailed discussion throughout the year. In vivo NMR is a rapidly developing new field for which regional biotechnology resources were thought to be most appropriate. The program's support of NMR imaging centers is believed noncritical for the development of this area, since many hospitals are purchasing this equipment with private funds. The future of HVEM resources continues under discussion, while the DRR also considers support of medium (400K) voltage electron microscope resources. In addition, the PROPHET computer resource was reexamined early in the year as the first step in the process of better defining its future directions. A group of advisors on PROPHET were scheduled to meet in October 1983 to begin a major redesign of the system.

- Short-term evaluations were made of both the Biomedical Research Support Grant and the Minority Biomedical Research Support Programs. Results of these studies, submitted at year's end, will be considered during the coming months, and their outcomes will be implemented with the advice of the Council and Review Committee.

- The policy regarding the threshold for eligibility for Biomedical Research Support Grants was examined; at the direction of the Congress, the threshold will be retained at $200,000. Awards were made in Fiscal Year 1983 using the $200,000 threshold.

- Several DRR programs considered the specific needs and uses for research training activities in their programs, including training in the use of laboratory animals, pre-doctoral training for minority individuals, and training of physicians in research methods. With the assistance of advisors, the Biotechnology Program staff developed a proposal to provide special training activities related to the use of technologies in biomedical research.

Among the most significant communications activities for Fiscal Year 1983, the Division's Office of Science and Health Reports planned, coordinated, and participated in six special events, including General Clinical Research Center 20th anniversary celebrations, press briefings, and a dedication. Former NIH Director Dr. Donald F. Fredrickson spoke to a filled auditorium at the University of Michigan during ceremonies marking that GCRC's 20th anniversary. Other 20th anniversary events were held at the University of Alabama in Birmingham, and at Boston Children's Hospital. The first GCRC located within a Veteran's Administration Hospital was dedicated at the University of Texas Health Science Center and the Audie L. Murphy Memorial Veteran's Hospital. Press briefings were held on treating kidney stone formation at the University of Texas Health Science Center GCRC, Dallas, and at the University of Pennsylvania Dental Clinical Research Center on the hazards of mercury poisoning for dentists.

During the year, the Division's publications, produced through its Office of Science and Health Reports and its Research Resources Information Center, won seven awards in the Society for Technical Communication's annual contest.

The STC is the world's largest professional organization dedicated to the advancement of technical communication. The awards included first place in the complete periodical category for the Division's newsletter, the Research Resources Reporter. An article from one issue went on to win additional honors in the STC's International Publications Competition. Finally, the American Dental Society awarded its 1983 second prize for science writing in the magazine division to the Reporter for an article on a GCRC dental clinical research center.

Animal Resources Program
Division of Research Resources

INTRODUCTION

The goal of the Animal Resources Program is to support resource projects that enable scientists to obtain and use animals effectively in health-related research. Special attention is given to those animal resource activities that support the missions of the various NIH components. The objectives are accomplished through the Regional Primate Research Centers Program and the Laboratory Animal Sciences Program.

REGIONAL PRIMATE RESEARCH CENTERS PROGRAM

The Regional Primate Research Centers Program was initiated by NIH in 1961. The original objective was to establish suitable facilities and appropriate research environments for conducting biomedical research that uses nonhuman primates. By 1965, seven Regional Primate Research Centers (RPRCs) had been constructed, equipped, and staffed. Each center is affiliated with a host academic institution and each has resources and research environments that are suitable for a broad range of biomedical research. The names and locations of the seven centers follow:

- o University of Washington RPRC, Seattle, Washington
- o Oregon RPRC, Beaverton, Oregon
- o Delta RPRC, Covington, Louisiana
- o Yerkes RPRC, Atlanta, Georgia
- o New England RPRC, Southborough, Massachusetts
- o Wisconsin RPRC, Madison, Wisconsin

The Animal Resources Program provides core operational support for the centers through resource grants. Research projects at the centers are funded largely by NIH categorical institutes, other Federal agencies, and private foundations through grants and contracts which are held by core staff and collaborative and affiliated scientists. Through their use of nonhuman primate models, these scientists have made numerous important contributions to biomedical research. During the past year, significant investigations have been carried out in various biomedical areas, including reproductive biology, infectious diseases, behavioral sciences, neurosciences, toxicology, nutritional and metabolic diseases, and environmental health.

During Fiscal Year 1983, core support in the amount of $19.619 million enabled a core staff of 141 doctorate-level scientists to conduct research in the centers. In addition, the resources and services of the centers were made available to 527 affiliated, collaborative, and visiting scientists from various academic institutions. Research training environments were provided for 210 graduate students engaged in thesis-related research. The program provided salary support for 608 doctorate-level, technical, and administrative staff personnel.

On a regional basis, the centers provided a total of 5,187 biological specimens to 319 scientists at research institutions throughout the United States. Scientific productivity within the seven centers has remained strong during the past year. The core staff and affiliated and collaborative scientists published 532 journal articles, books, and book chapters. In addition, 204 research abstracts were published.

Because of problems associated with obtaining certain species of nonhuman primates from countries of origin, all seven centers have continued their domestic breeding efforts. The 2,067 live births produced by the 7 centers in 1982 represented approximately 75 percent of their total primate animal requirements. Nuclear colonies of a number of less commonly used primate species also have been maintained to assure the survival of these species for potential future research needs. A total of approximately 13,500 primate animals, representing 43 species, were maintained by the centers in 1982 for research and domestic breeding uses.

Areas of research emphasis and examples of research activities at each center during the past year follow:

CALIFORNIA REGIONAL PRIMATE RESEARCH CENTER, UNIVERSITY OF CALIFORNIA AT DAVIS

The major research interests at the California center are environmental health sciences, infectious diseases, perinatal biology, behavioral biology, respiratory physiology, and immunology. An example of current research activities at this center is the work being done on simian acquired immunodeficiency syndrome.

Simian Acquired Immunodeficiency Syndrome

One of the most exciting projects in recent years at the California Center is that of simian acquired immunodeficiency syndrome (SAIDS). This syndrome was observed in a group of 64 rhesus monkeys which were maintained outdoors at the center. The syndrome, as in human AIDS, is characterized by general lymphadenopathy, severe opportunistic infections including cytomegalovirus (CMV) disease, chronic wasting, high mortality, and cutaneous tumors. Retrospective examination of colony records suggests that previous outbreaks have occurred at the center. In the current study, 24 of 64 animals have died. Peak mortality occurred six months after introduction into the cage. Affected animals have exhibited anemia, diarrhea, wasting, peripheral or

mesenteric lymphadenopathy, lymphopenia, splenomegaly, Kaposi-like tumors, fever, arthritis, bacteremia, depressed lymphocyte stimulation, and depressed serum protein levels. Evidence for the syndrome primarily is based upon pronounced lymphopenia, histopathology of spleen and lymph nodes, cutaneous anergy, CMV infections, declining immunoglobulin concentrations, and decreased mitogen stimulation. Collaborative studies between scientists at the center and at the Infectious Diseases Branch, National Institute of Neurological and Communicative Disorders and Stroke, NIH, have recently resulted in the successful experimental transmission of SAIDS from affected rhesus monkeys at the center to rhesus monkeys at NIH, Bethesda, Maryland. This new animal syndrome should serve as an extremely valuable model for human AIDS by providing insights into immune function, transmission of the disease, and the role toxic or viral agents may play in contributing to disease status.

DELTA REGIONAL PRIMATE RESEARCH CENTER, TULANE UNIVERSITY

The Delta center's research interests include microbiology and infectious diseases, immunology, parasitology, biochemistry, neurobiology, and urology. The affiliate and collaborative program covers additional areas, including vision research. An example of research activities at this center is the work being done on chronic pyelonephritis.

Studies on Chronic Pyelonephritis

Investigations by core staff scientists in the center's Urology Department have focused on chronic pyelonephritis, a disease which is reported to be the cause of chronic renal failure in up to 25 percent of children and young adults who are on dialysis or who have had kidney transplants.

Previous work has demonstrated that several species of nonhuman primates, including rhesus (Macaca mulatta) and cynomolgus (Macaca fasicularis), are excellent animal models for pyelonephritis studies. The role of bacterial infections of the kidney and the significance of vesicoureteral reflux in this disease have been examined. The studies have shown that reflux is not a major problem unless suitable pathogenic bacteria are present in the urinary tract. A much more important factor is bacterial adherence, which enables pathogenic strains of Escherichia coli to move up the ureter and establish renal infections. Strains of E. coli which possessed P-fimbriae were capable of adhering to specific receptors on the surface of the urothelium. Such strains were capable of reaching the kidneys and causing pyelonephritis. When the P-fimbriae were "neutralized" with chemically isolated receptors before the bacteria were inoculated into monkeys, pyelonephritis did not occur.

These findings open the door to the possibility of preventing or treating such renal infections by interfering with this adherence phenomenon. Extensive studies on the immunology of pyelonephritis in nonhuman primates demonstrated that the immune response was not responsible for renal scarring.

NEW ENGLAND REGIONAL PRIMATE RESEARCH CENTER, HARVARD UNIVERSITY

The New England center's core research interests are in the areas of microbiology and infectious diseases, psychobiology, comparative pathology, viral oncology, cardiovascular physiology, and nutrition. The center's extensive affiliate and collaborative research programs include numerous other areas of biomedical investigation. Examples of research activities at this center during the past year are the work being done on SAIDS and the correction of hereditary gene defects.

Simian Acquired Immunodeficiency Syndrome

The recognition of a naturally occurring immunodeficiency syndrome in macaque monkeys at the New England center represents a significant development. This syndrome has occurred primarily in Formosan rock macaques (Macaca cyclopis). Affected animals died with lymphomas (a rare disease in macaques) or such opportunistic infections as Pneumocystis carinii and Noma (necrotizing gingivitis).

These M. cyclopis exhibited anemia, neutropenia, and a circulating, bizarre, immature monocyte. In addition, liver function tests suggested hepatitis. The T4 (helper, inducer):T8 (suppressor, cytotoxic) ratio in the peripheral blood mononuclear T-cell populations of M. cyclopis in this colony were found to be decreased compared with those from either rhesus monkeys (M. mulatta) in the center's colony or from normal humans.

Certain similarities of this syndrome to human acquired immunodeficiency syndrome (AIDS) suggest that it may provide an important animal model for studies on AIDS.

Correction of Hereditary Gene Defects

Investigators in the New England center's Division of Microbiology have continued to explore the molecular basis for those unique properties of oncogenic viruses (Herpesvirus saimiri and Herpesvirus ateles) of nonhuman primate origin which enable them to induce malignant transformations. In contrast to other tumor virus systems (notably RNA tumor viruses), little is known on a molecular level about any herpesvirus-induced cell transformation or tumor induction. The structure of purified DNA from H. saimiri and H. ateles has been characterized and was demonstrated to be quite different from that of any other virus analyzed to date. Two independently derived non-oncogenic variants of H. saimiri were found to have lost a small segment of DNA in the same portion of the genome. The loss of this segment of DNA apparently does not affect the ability of the virus to multiply in cells permissive for virus growth, but infected animals do not develop tumors. Work in progress should determine the specific nature of the lesion in these non-oncogenic variants.

Use of recombinant DNA technology in the analysis of parental and non-oncogenic strains has led to the development of procedures that allow the precise introduction of deletions or foreign DNA sequences into the H. saimiri genome. This will allow researchers to use H. saimiri as a vector

for introducing specific genes into T lymphocytes for studying expression or correcting inborn gene defects.

OREGON REGIONAL PRIMATE RESEARCH CENTER, OREGON HEALTH SCIENCES UNIVERSITY

Major areas of research interest at the Oregon center include reproductive biology, perinatal physiology, cutaneous biology, immunology, nutrition, toxicology, and metabolic diseases and behavior. An example of research at this center is the work being done on spontaneous diabetes.

Spontaneous Diabetes

Investigations were continued on the spontaneous diabetes found in the center's colony of Celebes macaques (Macaca nigra) as a means of understanding this disease in humans. These animals showed a degeneration of some secretory cells in the islets of the pancreas. A study was performed to determine whether such degenerating cells release cytoplasmic antigens that would cause the immune system to produce islet cell antibodies (ICAs).

Macaca plasma was incubated with sections of baboon pancreas, and antibody reactivity against islet cells was examined by the peroxidase-antiperoxidase reactions of 30 non-diabetic monkeys. Eighty-seven percent were ICA-negative (ICA-), whereas all of the borderline diabetic or diabetic monkeys were ICA-positive (ICA+). Long-term diabetics were ICA-, presumably because of total loss of cells and their antigenicity. Of 23 hormonally impaired monkeys, 19 (83 percent) were ICA+. When ICA status was correlated with islet cell deterioration and amyloid deposition in biopsy and autopsy samples, 72 percent of the monkeys with no islet amyloid were ICA-, and 88 percent of the monkeys with minimal to moderate amounts of amyloid were ICA+. Thus, ICAs appear to be present at the earliest stage of lesion development, before clinical diagnosis of overt diabetes.

These results appear to be similar to those obtained in the aging human diabetic population and may provide a marker for identifying some forms of diabetes before clinical signs develop.

WASHINGTON REGIONAL PRIMATE RESEARCH CENTER, UNIVERSITY OF WASHINGTON AT SEATTLE

The core research program of the University of Washington center includes the areas of neurological sciences, cardiovascular function, developmental biology, disease models, endocrinology and metabolism, and craniofacial structure and function. An extensive affiliated scientist program involved more than 60 investigators engaged in a variety of research areas. An example of activities at the Washington center during the past year is the work being done on hearing loss.

Slowly Developing Hearing Loss in Rhesus Monkeys

It is well-recognized that high-level noise is a frequent cause of human deafness. The repeated exposure of people to moderate levels of noise over long periods of time also can lead to permanent hearing loss. The Occupational Safety and Health Administration (OSHA) currently permits humans to be exposed to 100-decibel sounds for 2 hours per day. A major problem in determining when there is a damaging noise in the environment occurs when initial stages of damage to the auditory system are often not detected by routine clinical hearing tests.

Investigations on rhesus monkeys (Macaca mulatta) at the Washington center have determined the relative sensitivities, by behavioral, physiological, and anatomical measures, in detecting the onset of hearing loss resulting from repeated exposure to moderate levels of sound. Systematic changes in the animals' hearing were related to changes in the way that nerve cells in the auditory nervous system react, and to the corresponding damage to the ear. Behavioral hearing was routinely monitored before and after hearing was temporarily lost by using 3-minute-per-day exposures to 100-decibel sounds (equivalent to many hair dryers or gas-powered lawn mowers). Two primate subjects participated in the standardized exposure sessions for 18 months; the remaining monkeys were exposed to identical stimuli for only 6 months.

No hearing losses were found in animals which had been exposed to the moderate sound levels for 6 months, but a significant high-frequency hearing loss was apparent during the final months of testing for animals exposed for 18 months. There were marked changes in the sensitivity of auditory nerve cell activity in those frequencies corresponding to the frequency regions where behavioral hearing loss was evident. However, sensitivity of some cells of the animals exposed for six months also demonstrated abnormal thresholds. Histological examinations of animals demonstrating hearing loss revealed corresponding widespread damage to the high-frequency region of the inner ear. The animals which exhibited only elevated cellular thresholds also had several small high-frequency lesions in the affected ears. These findings indicated that initially restricted cellular losses occur following very moderate sound exposures and are not reflected in traditional hearing tests.

WISCONSIN REGIONAL PRIMATE RESEARCH CENTER, UNIVERSITY OF WISCONSIN AT MADISON

Research areas at the Wisconsin center include endocrinology, behavior, neuroscience, reproduction, and pathology of environmental pollutants. An example of research performed during the past year is the work being done on endocrine and related changes associated with aging.

Endocrine and Related Changes Associated With Aging in Nonhuman Primates

Center investigators have determined that post-menopausal and ovariectomized nonhuman primates experience transient increases in skin temperature which are similar to the symptoms described for women experiencing hot flushes. This is believed to be the first demonstration of an animal model which may

be useful in studying the mechanism(s) responsible for debilitating vasomotor and related symptoms in older women. If these findings are confirmed through current research, this model system will be used to search for hypothalamic changes resulting from aging which may be responsible for vasomotor symptoms as well as alterations in endocrine function. An additional objective is to identify therapeutic measures, as alternatives to therapy with estrogen, which can be used to alleviate symptoms of hot flushes in women.

Other work in this area has included the study of transitional changes in the interactions between the hypothalamus-pituitary and ovarian systems in female monkeys as they progress through the aging sequence from normal adult menstrual cycles to menopause. This is a pioneering effort which is attempting to correlate several aspects of reproductive function and to identify changes which occur in different components at various stages of the aging process, using the same animals on a longitudinal basis. This effort represents the largest amount of accumulated data on this subject available for any primate species. It has great advantages over more limited studies with women, because the same animals are studied over long periods of time. In addition, detailed life histories are available for some animals, and the investigations are conducted under highly controlled conditions. Tentative interpretations of major malfunctions and their sequences have been made; however, additional studies are required for confirmation because of limited observations at the older ages.

YERKES REGIONAL PRIMATE RESEARCH CENTER, EMORY UNIVERSITY, ATLANTA, GEORGIA

Research interests at the Yerkes center include psychobiology of great apes and monkeys, anatomical and physiological aspects of the central nervous system, pathology, reproductive biology, immunology, language acquisition, and development of primate models of human diseases. An example of research activities at this center during the past year is the work being done on arthritis, amyloidosis, and yersiniosis.

Arthritis, Amyloidosis, and Yersiniosis in Nonhuman Primates

Yersiniosis, an enterobacterial disease caused by Yersinia organisms, has constituted a significant clinical problem in nonhuman primates at the Yerkes Field Station during recent years. Affected animals may become septicemic, with abcess formations in the spleen, mesenteric lymph nodes, and liver. Reactive arthritis and amyloidosis have also been noted in many advanced cases.

A study was initiated to evaluate the relationships between spontaneous Yersinia infections in the Yerkes Field Station nonhuman primate population and the subsequent occurrence of reactive arthritis and amyloidosis. Specific aims of the study include: 1) etiologic, epidemiologic, clinical, immunologic, and pathogenetic characterization of spontaneous yersiniosis, arthritis, and amyloidosis in nonhuman primates; 2) evaluation of the response of nonhuman primates to changes with Yersinia, particularly to the development of reactive arthritis or amyloidosis; and 3) documentation of the

histocompatibility antigen make-up of the rhesus monkey population housed in this environment to determine if specific RhLA types show increased susceptibility to these diseases, as has been documented in the human population for certain HLA types.

Observations to date show a continued high incidence of spontaneous Yersinia infection in this nonhuman primate population. The most frequently encountered serotypes are Y. enterocolitica 7,13 and 6,30 and Y. pseudotuberculosis serotype III. A significant number of wild rodents trapped in the environment have been shown to be carriers of Yersinia, with the most frequently encountered serotype being Y. enterocolitica 6,30. Arthritis, comparable to reactive arthritis of man, continues to occur with considerable frequency in this nonhuman primate population. Low antibody titers to Yersinia have been found in some cases of arthritis, and other studies suggest that immune complexes may be involved in the development of arthritis. Negative Yersinia cultures and serology in some arthritis cases, and the frequent isolation of Shigella and Campylobacter from this population, suggest that these organisms may play a causal role in the development of some cases of reactive arthritis in nonhuman primates, as is known to occur in man.

These studies may contribute to the development of a primate model for yersiniosis, reactive arthritis, and amyloidosis, which are common, debilitating, and sometimes fatal diseases in the human population. The histocompatibility antigen studies also should contribute to an improved understanding of genetic susceptibility to disease.

OTHER ACTIVITIES

Workshop On Acquired Immunodeficiency Syndrome in Nonhuman Primates

The Primate Research Centers Program sponsored a workshop on March 2, 1983, on "Acquired Immunodeficiency Syndrome in Nonhuman Primates." The purpose of this workshop, which was attended by approximately 300 scientists, was to discuss the clinical, pathological, and immunological findings related to recent simian acquired immunodeficiency syndrome (SAIDS) outbreaks with high mortality rates in macaque species (M. mulatta and M. cyclopis) at the California and New England Regional Primate Research Centers. Comparative medical aspects of this nonhuman primate disease at these centers and the human acquired immune deficiency syndrome (AIDS) were discussed. Sessions on differential diagnosis, epidemiology, and biosafety aspects of the disease were included. Although certain characteristics of the nonhuman primate disease SAIDS were noted to differ from those of AIDS, it was concluded that many of its characteristics (including lymphadenopathy, wasting, diarrhea, anemia, and severe opportunistic infections) are so similar that affected nonhuman primates may be extremely useful models for studies on human AIDS. It was strongly suggested that these investigations be continued and that other nonhuman primate colonies be carefully monitored to determine the possible occurrence of this disease.

During the eight months since this workshop was held, considerable progress has been made in SAIDS investigations at both the California and New England centers. Collaborative work between the California center and the Infectious Diseases Branch, National Institute of Neurological and Communicative Disorders and Stroke, NIH, has resulted in the successful experimental transmission of SAIDS by inoculating unexposed rhesus monkeys with tissue extracts from SAIDS-affected rhesus monkeys. The disease has also been experimentally transmitted at the New England center by inoculations of macaque lymphoid tissue. Results of the transmission studies have been published in the journal Lancet. Both centers have recently received categorical NIH research grant awards for continued studies on SAIDS. The other five primate research centers are continuing to evaluate their primate colonies by immunological studies and by examinations of clinical and necropsy records for evidence of this syndrome. To date, there has been no positive evidence of SAIDS in these five centers.

Demonstrations at the Primate Research Centers

The Mobilization for Animals (MFA), a coalition of various animal welfare and animal rights groups, held demonstrations against four regional primate research centers on April 24, 1983 (World Laboratory Animal Day). Attendance at the demonstrations was much smaller than had previously been forecast by the MFA. A total of approximately 6,000 people demonstrated at Boston, Massachusetts; Madison, Wisconsin; Davis, California; and Atlanta, Georgia. The demonstrations were peaceful in nature, and the important biomedical research being performed at these centers received a considerable amount of positive recognition by the news media. According to MFA literature distributed this year, as well as newspaper accounts, the MFA plans to hold demonstrations (24-hour vigils) at all seven centers in 1984. Demonstrations at other locations also are planned in an attempt to focus public attention on psychological experiments on animals which allegedly involve stress and pain.

LABORATORY ANIMAL SCIENCES PROGRAM

The Laboratory Animal Sciences Program (LASP) assists institutions in developing and improving animal resources for biomedical research and training through the award of research and resource grants and contracts. Program areas include support for research related to important laboratory animal disease problems; animal colonies which serve as national resources for biomedical research; studies directed at finding animal models which are needed for research on human diseases; institutional animal resource improvement projects to help upgrade animal facilities and develop centralized programs of animal care; laboratories for the diagnosis and control of diseases of laboratory animals; and training of specialists in the field of laboratory animal medicine. In Fiscal Year 1983, the program awarded funds totaling $8,602,598, which supported 54 grants and 3 contracts relevant to animal research or resource activities, 10 institutional training programs, and 3 individual fellowship awards.

RESOURCE-RELATED RESEARCH

The majority of these projects involve investigation of the etiology, pathogenesis, and control of laboratory animal disease problems. For example, current projects include the diagnosis and control of mammalian encephalitozoonosis, control of respiratory mycoplasmosis in rodents, experimentally induced mucoid enteritis in rabbits, and development of a live vaccine for the control of pasteurellosis in rabbits. The last project is of particular importance because pasteurellosis is the primary cause of death in weanling and young adult rabbits and a common complication in experimental situations. During the first year of work on this project, the prevalence of various serotypes of P. multocida isolates from healthy and diseased rabbits was established, and the pathogenesis of one major serotype was studied. Preliminary studies with a streptomycin-dependent P. multocida live mutant vaccine demonstrated a local and systemic immune response following intranasal inoculation.

In addition to disease-related studies, several projects involving population studies, classification, and breeding of nonhuman primates are currently active. The population studies include a long-term evaluation of natural rhesus populations in northern India and definition of important habitat features for West African rain forest primates. Extensive field work in Peru, Brazil, and Colombia and study of museum specimens are currently under way as part of a comprehensive project to establish definitive taxonomies of the various cebid monkeys, with particular attention to two species of significance to biomedical research: Saimiri (squirrel monkeys) and Aotus (owl monkeys). The current taxonomic classification of these species is confusing and incomplete. Preliminary taxonomic revisions prepared during the past year were based on more than 1,000 specimens of Aotus and Saimiri. Publication of the preliminary taxonomies will provide investigators with a much-needed capability for identifying the species and subspecies and a knowledge of their exact geographic distribution. The eventual goal is to publish the information as volume two of Living New World Monkeys. Volume one dealt with Callitrichidae, the family that includes marmosets and tamarins.

Another project involves genetic investigations in rhesus monkeys at the Wisconsin Regional Primate Research Center. In particular, additional genetic markers are being sought in order to develop a multiple-locus measure of inbreeding. Two recently developed typing reagents, a complement (C3) polymorphism and an isozyme system (catalase III), have greatly increased the resolving power of disputed parentage tests. This is of practical significance because it clearly demonstrates that, although the dominant male in a captive troop of rhesus monkeys participates in most inseminations, he does not necessarily sire the most offspring. A major goal of current work is to complete development of "Colony Sim," a discrete-time, event-oriented micro-simulation model that will permit experimentation with the demographic, mating, and genetic structure of captive animal breeding colonies. The model which is now being validated will provide a means of evaluating various colony management practices. When completed, it will allow scientists to

answer such questions as: What is the minimum practical colony size that can support long-term population survival, and which harvest schedules will best serve the demographic and genetic goals of a particular colony?

The number of resource-related projects has remained relatively constant in recent years (9-12 active projects). There is growing recognition that naturally occurring laboratory animal diseases and environmental factors can have a significant effect on research projects. This year, four new projects were awarded. The first is aimed at a better understanding of antiphagocytic resistance mechanisms of Pasteurella infection in the rabbit; the second will examine the effects of various light intensities on retinal photoreceptors of albino rats; the third will study the effects of Sendai virus in resistant and susceptible mice; and the fourth will support the development of a technique for rapid diagnosis of Herpesvirus simiae (B virus) and preliminary studies of a possible subunit vaccine. Herpes B virus infection is a common infection of macaque species, and human infection, although rare, has a high mortality rate. Current serologic tests do not differentiate between several herpes viruses, and production of type-specific antibodies using HSV-specific glycoproteins will allow the development of a reliable test.

A new focus of research activity was initiated this year under provisions of the Small Business Innovation Research Development Act of 1982 (Public Law 97-219). This amendment to the Small Business Act required Public Health Service agencies to set aside a specified amount of their research and development (R&D) budgets for a Small Business Innovation Research (SBIR) Program. In Fiscal Year 1983, the amount set aside for the Animal Resources Program was $80,000. The legislation was intended to stimulate technological innovation, use small businesses to meet federal R&D needs, increase private-sector commercialization of innovations derived from Federal research and development, and foster and encourage participation by minority and disadvantaged persons in technological innovation. For purposes of the SBIR Program, a "small business" was defined as any organization that is independently owned and operated for profit, not dominant in the field in which it is operating, with 500 or fewer employees.

The SBIR Program consists of three phases. In phase one, the technical merit and feasibility of R&D ideas are established. In phase two, the proposed R&D ideas that are likely to result in commercial products or services are developed in detail. In phase three, private capital is obtained, where appropriate, to commercialize the results of the R&D.

The first SBIR grant application receipt date was May 1, 1983, for phase one proposals. The Animal Resources Program received 13 proposals, which were reviewed by study sections meeting in July and by a special meeting of the National Advisory Research Resources Council on September 12, 1983. Of the 13 proposals, 7 were approved and 1 was funded ($47,283). The funded project will search for structure-activity relationships that would be capable of predicting the skin and eye irritant properties of chemical compounds of known structure. The successful development of structure-

activity equations (models) for the Draize skin and eye irritancy test would mean that some pure compounds would not need to be tested in animals.

There will be two receipt dates for phase one applications in Fiscal Year 1984 and one receipt date for phase two applications.

ANIMAL MODELS AND SPECIAL COLONIES

The goals of the Animal Models and Special Colonies Program are: (1) to define, characterize, and make use of the relevant biological attributes of selected animals which display potential for use in biomedical research and (2) to establish, improve, or expand special colonies of well-characterized animals which are of proven value for biomedical research, but which are not generally available from other sources.

In regard to the first objective, an active resource at Washington State University involves a multidisciplinary effort to identify, characterize, and make available new animal models of human genetic diseases. Potential models are sought from a variety of sources, including animal clinics, veterinary practitioners, and breeding associations and clubs. This group has worked with 30 animal models or potential animal models during the past 5 years and has identified 7 new models during this period. Some models are now well-established and have separate grant support. Others are still in the early stages of development. During the past year, emphasis was placed on: Chediak-Higashi syndrome in cats; inherited feline tremors; combined immunodeficiency in horses; canine juvenile diabetes mellitus; lysozyme deficiency in rabbits; malamute chondrodystrophy; canine type II fiber myopathy; and inherited canine myasthenia gravis.

The last project is representative of the general approach taken. A colony of approximately 50 dogs has been established. Analysis of breeding data indicates that inherited canine myasthenia, a motor endplate disorder, is transmitted as an autosomal recessive trait. The onset of the disease is early and is apparent in 8- to 12-week-old puppies. The clinical features are generalized muscle weakness which worsens after exercise and which improves after administration of anticholinesterase drugs. Current studies are aimed at identifying the ultrastructural features of the motor endplate, the number of endplates, using a snake venom neurotoxin that binds specifically to endplates, and receptor antibody levels in the affected dogs. To date, it appears that antibodies are not formed to the acetylcholine receptor in these dogs, as they are in the adult acquired autoimmune form of myasthenia gravis in humans. The number of receptors is markedly reduced in the dogs, however, as it is in the inherited form of myasthenia gravis. Research activities of the resource during the past year were documented in 35 papers published or in press. Animals supported by the resource provided a valuable source of material for graduate study, including research projects by two postdoctoral students, four Ph.D. candidate students, and five Master candidate students.

Other animal model projects are conducted using selected species which have potential utility as models in more than one categorical area of research. Several marine invertebrate projects involving loliginid squid and octopuses, for example, are designed to develop a system and methodology for large-scale culture of these species for biomedical research. The nervous system of the octopus is highly advanced, and our knowledge of the physiology and behavior of Octopus is more comprehensive than for any other marine invertebrate. The great bulk of this work has been done in Europe, where O. vulgaris occurs in large concentrations that are fished commercially.

In the United States, little work has been done because none of the species occurs in large, easily harvested populations along the coast. Thus, attainment of this project's goals will result in the addition of an important species to the repertoire of animals available for the elucidation of many biological principles. Results after just two years are highly encouraging. Sources of wild-caught eggs or gravid females have been found for several species; small-scale culture of two species was completed; large-scale culture of two species is under way; and several live food organisms that can be used to rear octopuses were developed as an alternative to mysid shrimp. Cannibalism proved to be the major cause of mortality with one species, leading to its replacement by a less aggressive species for the current large-scale culture efforts. Future work will concentrate on completing current culture efforts, formulating an artificial food ration, and encouraging the use of laboratory-reared octopuses for behavioral and physiological experiments.

Special colony projects combine in varying degrees the maintenance and production of special strains or stocks of animals with ongoing research to further develop and characterize the models. Currently supported projects include a bullfrog (Rana catesbeiana) resource at Louisiana State University and a mouse mutant gene resource at the Jackson Laboratory.

The mouse resource colony at the Jackson Laboratory originally included some 140 mutants with a focus on endocrine, neurological, and immunologic problems. The specific aims are to maintain these well-defined stocks, to discover and characterize new mutations in the mouse, and to develop stocks of new and established mouse mutations for use as animal models in biomedical research. During the last 4 years, more than 11,000 mice were distributed to investigators either as breeding stock or experimental animals. A charge is made for this service, and the funds are returned to the grant. The primary source of new mutations is the main breeding colony at the Jackson Laboratory, which raises more than 2 million mice a year. As an example of the screening process involved in finding new mutations during the last project period, a total of 196 phenodeviants (representing about one-tenth of the number observed) were considered worthy of additional investigation. Those animals, together with their normal siblings and parents, were obtained by the resource. Each was tested to determine whether the deviation was inherited, and if so, to determine the mode of inheritance. Of these, 107 were not recovered in future generations, 59 were recovered but discarded, and 30 were recovered and kept for further testing.

This effort resulted in the characterization of a number of new mutations, including the first Y-linked variant found in mammals involving testis determination; "twitcher," an autosomal recessive mutation characterized by myelin degeneration and macrophage inclusions resembling those seen in globoid cell leukodystrophy (Krabbe's disease); "stumbler," an autosomal recessive mutation that affects balance; an inherited hypothyroidism; and an autosomal recessive mutation located on Chromosome 1 that is characterized by an early-onset, autoimmune disease with massive lymphoproliferation.

Support for projects related to animal model development and the establishment of special animal colonies has decreased in recent years as depicted in the following chart.

	Total Active Projects	Dollars Awarded*	Percent of Budget
FY 80	24	1,912	25
FY 81	15	1,623	23
FY 82	12	1,055	14
FY 83	7	889	11

*In thousands

This reduction is in keeping with the DRR Five-Year Plan, which provided for decreased emphasis in this area, particularly of special colony projects if funds were reduced for the program.

OTHER PRIMATE RESOURCES

In addition to the seven regional primate research centers, the Animal Resources Program supports several other nonhuman primate resources. These include one contract and four grants for the domestic breeding of nonhuman primates. In addition, there is a grant for a Primate Supply Information Clearinghouse. These projects are part of the effort to provide a supply of primates for essential biomedical research in the face of export restrictions and embargoes by countries of origin. The contract for production of rhesus monkeys scheduled for phase-out in 1982 has been terminated. The one contract remaining is programmed to produce about 550 rhesus and 100 cynomolgus monkeys per year. As of June 30, 1983, there were 763 female rhesus breeders and 125 cynomolgus female breeders in the production colony. There were 767 rhesus births and 56 cynomolgus births this past year. There were 800 rhesus monkeys and 61 cynomolgus monkeys sold from the colonies. In addition, 731 rhesus monkeys were transferred to other Public Health Service programs for the cost of shipping. The only requests that cannot be met are

for young adult and adult males. Production from the remaining colony is expected to meet current needs for research.

The grant-supported primate breeding projects are designed to establish nuclear production colonies and to determine proper husbandry techniques for maintaining these colonies. Colonies under development are baboons, squirrel monkeys, and two species of Galago (bushbabies). The baboon project is the most fully developed. The population now includes 224 females, 33 males, 191 juveniles, and 179 infants of Papio cynocephalus anubis (olive baboon) and 24 females, 2 males, 40 juveniles, and 12 infants of Papio cynocephalus cynocephalus (yellow baboon). In addition, nuclear breeding colonies of P. c. hamadryas and P. c. papio have been established. A genetic monitoring program has been initiated which includes development of a battery of biochemical genetic markers for determining the extent of genetic polymorphism and parentage relationships in the founder population. Such information will provide a genetic basis for deciding which animals to maintain as breeding stock and which best fit the needs of potential users while protecting the colony from the deleterious effects of inbreeding. The breeding effort is currently far enough along that three species of colony-born, juvenile baboons and a limited number of adult baboons are available for sale. A time-pregnant breeding program was recently established to meet the specific needs of one National Institute of Child Health and Human Development grantee.

In addition to these breeding and development grants, the Caribbean Primate Center at the University of Puerto Rico has a grant supporting an island colony of more than 1,000 rhesus monkeys. These monkeys have genealogy records dating back to 1938, making them very useful for social and behavioral studies. The center also is conducting some pilot studies on tropical diseases and physiology with primates housed on the mainland. The National Institute of Neurological and Communicative Disorders and Stroke maintains a colony of rhesus monkeys at the center for fetal studies.

The Primate Supply Information Clearinghouse is designed to facilitate maximum research utilization of primates already in this country. The clearinghouse matches requests for primates, primate tissues, and related services with investigators who and breeding colonies that have these items available. The clearinghouse publishes a weekly bulletin (circulation of 1,365) and handled 1,431 formal requests for primates and 1,888 informal requests during Fiscal Year 1983. It placed 5,033 living primates and satisfied 119 requests for cadavers, tissues, and other specimens and 28 special listings for cages, services, etc. The increase in listings, genera, and species placed may reflect a loss in funding by a substantial number of established projects. The clearinghouse has responded well to the decrease in support for projects by making alternative arrangements for the animals involved.

INSTITUTIONAL ANIMAL RESOURCE IMPROVEMENTS

Institutional animal resource improvement projects are awarded to help institutions upgrade their animal facilities and develop centralized programs

of animal care to support their biomedical research programs. A major objective is to enable institutions to comply with the Animal Welfare Act and DHHS policies on the care and treatment of animals. Requests of this type are usually for animal cages to meet current regulations, general sanitation equipment such as cage washers, renovation of animal facilities, and addition of trained professional and technical personnel. The projects are supported for one to three years, after which the applicant institution is expected to take over complete financial responsibility for its basic animal resource.

Institutional improvement projects have been supported since the inception of the Laboratory Animal Sciences Program. This area received increased emphasis in Fiscal Year 1972, when Congress appropriated an additional $1.5 million to help research institutions achieve compliance with the Animal Welfare Act of 1970 (Public Law 91-579). The NIH policy on "Care and Treatment of Laboratory Animals" (issued June 14, 1971) and the subsequent DHHS policy on "Animal Welfare" (issued May 14, 1973) also contributed to the overall response in this area. During the past 13 years, 122 institutions have received improvement grants, with awards totaling approximately $16.8 million. The following table shows the levels of activity in recent years.

FY	Reviewed	Approved	New Awards	Total Active Projects	Dollars Awarded*	Percent of Budget
71	9	5	1	14	673	11
72	21	15	19	24	2,169	35
73	86	62	15	28	2,318	37
74	19	12	36**	46	3,217	55
75	21	17	19**	38	2,582	42
76	19	9	6	21	1,259	22
77	14	7	6	13	1,054	19
78	21	13	3	11	793	12
79	9	7	4	7	709	11
80	12	8	4	6	783	10
81	16	16	2	7	298	4
82	17	16	5	7	697	10
83	4	4	2	2	229	3

*In thousands
**Includes applications reviewed in previous year

The chart indicates a relatively steady rate of new proposals until Fiscal Year 1983. There is still considerable interest in this program area and substantial institutional need for assistance, as indicated by the National Survey of Laboratory Animal Facilities and Resources (published March 1980; FY 1978 data). In recent years, however, emphasis has been placed on funding new projects of other types and on combating inflationary costs. Recognition that institutional animal resource improvement awards were limited resulted in a decrease in the number of new applications. Specific budget proposals have been made in the Animal Resources Program in recent fiscal years, including this year, for major new funding in this area. Support for new construction has also been requested.

RESOURCE LABORATORIES

The objectives of resource laboratories are to provide improved animal health programs through appropriate surveillance activities and investigation of naturally occurring disease and other laboratory animal problems; to support studies resulting in new information on diseases of laboratory animals and their etiology; to aid in the elucidation of new animal models of human disease; and to develop resources for research and training. Resource laboratories have been a major program activity for more than 10 years. Most resource laboratories are institutional in nature; however, in several instances more than one institution in a metropolitan or regional area has been served. There has been a continuing turnover in the institutions receiving such awards (support has been terminated for 14 laboratories). The total number has remained relatively constant (13-16) in recent years. Approximately 38 percent of the budget is awarded in this area.

Laboratory activities range from surveillance and monitoring to conduct of research on important laboratory animal disease problems. One new laboratory was able to initiate several quality assurance projects aimed at intercurrent laboratory animal disease problems. For example, the use of sentinel rodents placed in rooms which housed only vendor animals revealed that the barrier system in use was not sufficient to maintain specific-pathogen-free (SPF) status for rodents. The major problem appeared to be investigator contamination of the SPF rooms. Accordingly, the barrier operation is being redesigned to increase security.

Increased sensitivity of assay systems to recognize the presence of a variety of pathogens is of vital concern to all the laboratories. Application of Enzyme-Linked Immunosorbent Assay (ELISA) procedures to the recognition of murine cytomegalovirus (MCMV) and Corynebacterium kutscheri was reported by one laboratory. Because MCMV can have significant long-term effects on the immune system, it now appears feasible to test for antibody to this agent in mouse antibody screening protocols. Likewise, the early detectability and heightened sensitivity with ELISA are extremely important for C. kutscheri, because of its potential to cause high morbidity and mortality in rats.

Another laboratory has been evaluating the specificity and sensitivity of immunofluorescence (IF) procedures, ELISA tests notwithstanding. A current offshoot of this project was the development of "spot-slides" for the qualitative diagnosis of murine viral infections. Early indications are that this procedure is at least as rapid, sensitive, and specific as existing ELISAs and, for some viruses (e.g., reovirus-3), superior to ELISA. The procedure involves seeding virus-infected cells to microscope slides and fixing them for immunocytochemical staining. A drop of test serum on each "cell spot" is tagged with fluorescein-conjugated antibody and viewed with a uv microscope. Stained cell spots indicate that homologous antibody is present in the test sample; unstained spots indicate that antibody is not present. The test takes less than two hours to perform. This procedure probably will be available for field testing during the coming fiscal year.

One laboratory examined the effect of shipping stress on immunologic functions in mice. The mice were shipped either by truck or by plane, two of

the most common modes for transporting animals. While mice were in transit, temperature fluctuations and light intensity were monitored. The foot pad test, hemagglutination assay, and plaque-forming cell assay were used to measure immunologic function. Regardless of the method of shipment, corticosterone values in the mice were markedly increased at arrival and remained high for a 48-hour period. Immune-function assays were significantly lessened in the mice at arrival but returned to baseline within 48 hours, indicating that a minimum 48-hour stabilization period is required for all new arrivals.

One resource laboratory conducts a program in conjunction with the Department of Biological Safety and the Division of Animal Care to test for infectious contaminants in cell lines and transplantable tumors destined for animal inoculation. Recently, seroconversion to lymphocytic choriomeningitis virus (LCMV) was detected in several mice from a specific-pathogen-free inbred mouse colony during routine quality assurance monitoring. The colony is used to test newly synthesized chemotherapeutic agents on a battery of transplantable tumors. Clinicians found that several tumors used in the room had been received from another research institution and had been passaged into mice by the laboratory supervisor before specimens had been submitted for virological testing.

The laboratory responded by designing an accelerated testing program to recheck all transplantable tumors in the laboratory on a cost-sharing basis. Because the laboratory has full, on-line capabilities and has developed rapid in vitro techniques for virological testing, results for each tumor were available in several days. This enabled the investigator to passage tumors into new syngeneic recipients before donors succumbed, thus significantly reducing the lag time for reconstituting tumor stocks and for reinitiating chemotherapeutic trials. Several tumors contaminated with LCMV or MHV were discarded, and the room holding LCMV-positive animals was quarantined, depopulated, and reset. Suspect aliquots of tumor that had been distributed to other laboratories were recalled and discarded. Such a service is important because this program acts as a resource for distribution of tumor cell lines throughout the country.

Although bacterial infections are important in laboratory animal medicine, they rarely occur as epizootics with significant morbidity and mortality. An exception to this was encountered by one laboratory during the past year, when a beta-hemolytic streptococcus was associated with large numbers of acute deaths in experimental dogs. The dogs were not conditioned animals and were obtained from two commercial suppliers. Animals from this group were found dead or in severe pulmonary distress. Autopsy of the animals showed a syndrome characterized by a hemorrhagic bronchopneumonia which involved extensive portions of the lungs. Microscopically, the lesions were seen to be necrotizing, and gram-positive cocci were found in the upper airways, the lungs, and in other tissues, in some cases. The animals at the facility were then screened for the presence of beta-hemolytic streptococcus, which was consistently cultured from autopsied animals. Several were found to harbor this organism in their pharynx.

While Streptococcus zooepidemicus has been reported to be a cause of infection in dogs, it has not previously been observed to cause disease of this severity in such large numbers of apparently otherwise healthy animals. Its significance for the research community is obvious, because it resulted in the loss of many animals as well as many hours of professional and diagnostic time. Recognition of the disease has proved important in that it can be controlled by appropriate management and antibiotic therapy.

Another laboratory recognized asymptomatic Salmonella contamination in animals coming from one commercial rat breeder's barrier facility. This resulted in a decontamination effort and the sacrifice of 35,000 rats, thus preventing the weekly introduction of thousands of latently diseased rats into research laboratories nationwide. Subsequent investigation traced the source of the infection to a rodent feces-contaminated well casing outside of the barrier.

Recognition of potential animal models is an important aspect of working up problems presented to the laboratory. One resource evaluated a young Balinese cat with progressive neurological dysfunction. The clinical, morphological, and biochemical findings suggested that this cat had a sphingomyelin lipidosis similar to human Niemann-Pick's disease type A. Because the parent cats are available, laboratory perpetuation of this mutation for research is under way. It appears that this feline model of a human lysosomal storage disease will be of extraordinary value for research on the pathogenesis and therapy of this group of diseases.

In conjunction with colleagues in neuropathology, another laboratory has been studying a colony of dogs with cerebellar degeneration to document the phenotypic expression of this condition, to analyze the mode of inheritance, to carry out biochemical screening tests in infected animals, and systematically to assess the pathology of the disease. To this point, the clinical disease has been studied in 8 adult Gordon Setters, 3 years or more of age, and the progression of the disease was monitored from birth to 27 months. A variety of clinical signs, related principally to cerebellar function, were observed to develop and increase in severity as the dogs became older.

Material from the dogs has been provided to several other medical centers to compare with material from human patients. Neuropathologic studies have shown the cerebellum to be selectively involved with a decrease in thickness of the molecular layer and reduction in Purkinje and granular cell populations. These are similar to changes described for human cases. These morphologic studies have been coupled with studies of receptors and neurochemical markers. In many ways, canine inherited ataxia reflects the clinical pathologic changes seen in slowly evolving human inherited ataxias and provides an opportunity to study the sequence of changes in transmitter-specific cell populations.

The most recent addition to the diagnostic resources, at the Marine Biological Laboratory, Woods Hole, Massachusetts, has been busy establishing

a program of marine animal health that includes education of investigators about the importance of disease problems. Demonstration of the presence of specific disease entities has increased awareness and recognition of the need for animal health standards with laboratory marine animals. A program of animal health surveillance and record-keeping has been developed. Routine water quality tests have been established, and mortality associated with failure to control water temperatures has been identified. Traumatic injuries to wild laboratory-maintained marine animals were the greatest direct and indirect predisposing causes of mortality last year. Trauma occurs during harvesting, transportation, and laboratory maintenance and is influenced by how a species is captured, anatomic predisposition to injury, and population density in the aquaria. Bacterial infection was the second major cause of mortality, and several new specific disease problems and their bacterial causes were reported. Parasitism was also an important cause of mortality in marine species, and the importance of a number of parasites as serious pathogens was demonstrated.

OTHER RESOURCE ACTIVITIES

The Laboratory Animal Sciences Program (LASP) provides partial support for the Institute of Laboratory Animal Resources (ILAR) of the National Academy of Sciences and for the accreditation program of the American Association for Accreditation of Laboratory Animal Care. The former project serves the biomedical community by providing scientific and technical information on laboratory animal resources, including guidelines for animal care, use, and breeding; planning and conduct of conferences and symposia; and promotion of high-quality, humane care of laboratory animals. ILAR carries out its program through a small staff and through committees of recognized scientists and experts from the scientific community. General support also is received from a number of other government agencies.

Other information projects of the LASP include support for the Laboratory Primate Newsletter and the Registry of Specialized Genetic Stocks. The latter project collects and periodically updates a registry which lists genetic stocks of chickens, Japanese quail, and turkeys that are maintained in the United States, Canada, and more than 15 other countries. The most recent directory included the description and location of 209 chicken, 50 quail, and 13 turkey specialized lines and strains; inheritance, linkage and literature data; chromosome linkage maps; descriptions and location of 591 breeds and varieties; and a breeder/supplier index. Approximately 633 NIH-funded research projects ($54.9 million, FY 1981) use birds.

The LASP currently supports two reference center projects. The first is the Registry of Comparative Pathology, located at the Armed Forces Institute of Pathology. The registry has continued to augment its collection of specimens from primates and other laboratory animals, domestic and wild animals, fish and birds (more than 660 accessions during the last reporting period). Material has been made available to others and used in the preparation of exhibits, lantern and microscopic slide sets, and as the basis for a number of publications. The registry responds to numerous outside requests for

consultation and publishes a quarterly Comparative Pathology Bulletin to promote communication and information dissemination to the biomedical community, which it mails to over 3,750 addressees. Since 1972, it has been responsible for preparing one or two descriptions of an animal model of human disease for publication each month in the American Journal of Pathology. A handbook, entitled Animal Models of Human Disease, has been prepared for sale. Eleven fascicles covering 258 models, with a cumulative index, have been published so far. In April 1983, a symposium on the "Comparative Pathobiology of Major Age-Related Diseases: Current Status and Research Frontiers" was co-sponsored with Universities Associated for Research and Education in Pathology, Inc. Also, an annual 3-day course in comparative pathology was offered for the 10th time in May 1983.

A relatively new reference center activity is located at the Jackson Laboratory. Entitled "Cryopreservation of Murine Germplasm," the long-term objective of this project is to establish a bank of frozen mouse embryos to preserve mutants and strains of mice that are valuable to many fields of research. In many cases, cryopreservation will allow a reduction in the number or size of colonies maintained by conventional breeding procedures and will also serve to retard genetic drift. Freezing techniques, using eight-cell embryos, frozen at a controlled rate and stored in liquid nitrogen, are now well-established. More than 200,000 embryos have been frozen and stored from approximately 300 different strains since the project's inception 2 years ago. To date, 48 strains have been terminated from active breeding because embryos have been safely preserved. Three strains have been reconstituted on request.

MANPOWER DEVELOPMENT

Training in laboratory animal medicine is intended to prepare individuals to provide professional care for the many species of laboratory animals, to manage central animal resources, and to give special assistance to investigators through knowledge of laboratory animal biology and understanding of research methods. In addition, trainees are prepared to participate in the teaching of graduate students and young investigators and to pursue their own research interests, either as independent investigators or as members of a research team.

Currently, there are 9 active (T32) institutional postdoctoral training programs with a total of 32 funded trainee positions. One institutional short-term (summer) training program also is funded. Three individual postdoctoral fellowships also were supported during the fiscal year. Because the average training period of the postdoctoral programs is 2 1/2 years, there are usually 8-10 graduates per year. Currently available figures indicate that 189 trainees and fellows have completed training since the inception of the training grants and fellowships in laboratory animal science and medicine. Sixty-six of these are employed by medical schools and 75 by other academic, research, or governmental organizations. The majority (112) are serving as directors or staff members of a vivarium; 62 are engaged in teaching and research or are obtaining additional training; and 15 are in

public health, private practice, or retired. Retention in the field of laboratory animal medicine has been excellent, emphasizing the career orientation provided by the training and the continuing need and opportunities available for such individuals.

For the past eight years, the active training programs and diagnostic resources have been encouraged to employ veterinary students during their summer break. Over the past year, 12 programs involving 25 students participated. Critiques of the students involved were submitted to the program and, in turn, distributed to all the program directors. It appears that such work experience is resulting in greater knowledge and interest in the field of laboratory animal medicine by veterinary students. Several former summer students entered formal postdoctoral programs this year, and development of a "pool" of such individuals for future postdoctoral training should result in long-term benefits to the field.

As the specialty field of laboratory animal medicine has matured, it has become apparent that many of its members find, upon completion of their training, that the demands for research resource activities have been overwhelming. Further, most recent graduates do not have the depth of research experience in a particular discipline to allow them to compete for regular research grants. To meet the need for additional experience and time for full-time research, a new research career development program, the Special Emphasis Research Career Award (SERCA) in Laboratory Animal Science, was established in 1982. This special award offers in-depth experience for the laboratory animal specialist in various fundamental and clinical scientific disciplines. It is made to develop multidisciplinary veterinary researchers who will direct their research toward refining the use of laboratory animals in biomedical research, the study of significant laboratory animal disease problems occurring in vivarial settings, and the development of new animal models useful in solving biomedical research problems. During Fiscal Year 1983, a total of 10 SERCA applications were received; 8 were recommended for approval, and 4 were awarded. The research areas the four awardees will concentrate on are immunology, toxicology, virology, and immunogenetics.

Future Directions

The Laboratory Animal Sciences Program plans to increase its support for projects aimed at the etiology, pathogenesis, diagnosis, and control of significant laboratory animal diseases. Because of the large numbers of rodents used in research and the demonstrated impact of many of these diseases, projects will focus on viral diseases in rodents. Animal model and special colony projects have decreased in recent years. Support for primate breeding activities will continue to be shifted to the user community. The ability to fund institutional animal resource improvement projects will depend upon the appropriation of additional funds for this activity. The current number of diagnostic resources and institutional training programs will be continued. Manpower development will be emphasized through individual fellowships and the SERCA program to the extent funds can be made

available for this purpose. The full impact of the Small Business Innovation Research (SBIR) Program on these activities remains to be determined. The amount set aside in Fiscal Year 1983 under the SBIR Program was based on 0.2 percent of the Animal Resources Program appropriation. This set-aside will increase in future years (FY 1984, 0.6 percent; FY 1985, 1.0 percent; FY 1986 and 1987, 1.25 percent).

ADMINISTRATIVE ISSUES

Revision of the Guide for the Care and Use of Laboratory Animals was begun in late 1982 by a committee appointed by the Institute of Laboratory Animal Resources, National Research Council. It has been five years since the Guide was revised. The revision is to be completed at the end of 1984.

The revision committee, consisting of seven veterinarians and eight users of laboratory animals, was appointed in spring 1983 and held its first meeting in May. A public hearing was held in Washington, D.C. Two subsequent public hearings, in San Francisco and Chicago, also were held. All three hearings were well-attended by members representing animal humane societies and the general public. More than 50 witnesses appeared before the committee to give their views about the revision of the Guide. Numerous written comments were received. The public hearings not only sparked public interest but also improved communications between those concerned with professional care of laboratory animals and those concerned with their general welfare.

The committee meetings have been well-attended by the membership, with excellent leadership from its chairman, Dr. Steven Pakes of the University of Texas, Dallas. Draft manuscripts of the revised Guide will be reviewed by the committee in early 1984.

The Trans-NIH Coordinating Committee on Research Animal Resources met seven times in Fiscal Year 1983 to exchange information on such issues as laboratory animal use data, regulation of the use of laboratory animals, activities of animal welfare organizations, proposed changes in NIH policy regarding research animals, and Federal legislative developments.

Throughout the year, the committee received briefings from representatives of the Animal and Plant Health Inspection Service, U.S. Department of Agriculture, and from various components of the NIH. Such exchanges of information have served to heighten the awareness of the animal welfare issue in both the NIH intramural and extramural communities, and to improve communications between the two. During the coming fiscal year, the committee will be involved in reviewing and advising NIH on its efforts to inform the general public about the care and use of research animals. The committee also will work with the Office for Protection from Research Risks to design training programs to improve the effectiveness of university administrators and to inform investigators about NIH policies on the care and use of research animals.

There has been considerable Federal activity on proposed legislation to increase regulation of the use of laboratory animals. Bills have been sponsored by Congressmen Walgren, Waxman, Dole, and Melcher, and a resolution has been sponsored by Representative Lantos. The Animal Resources Program was kept up to date on this legislation by the Division of Legislative Analysis, and program participants attended several congressional hearings. Although no specific legislation was enacted during this session, it seems obvious that there will be increasingly stringent Federal requirements for the housing and care of laboratory animals, for the review of research protocols using animals by animal care committees, and for inspection and certification by Federal or private agencies of animal care programs in universities and other research institutions.

Table I

Primate Research Centers Program Applications - FY 1983

Application Types	Number Rec'd	Amount Requested 1/	Number Appr	Amount Approved 1/	Number Funded	Amount Funded 2/
New.....	-	--	-	--	-	--
Renewal.....	2	6,528,563	2	6,084,244	2	5,153,453
Supplemental.....	-	--	-	--	-	--
Continuation.....	5	13,357,836	5	12,612,202	5	14,465,552
TOTALS	7	19,886,399	7	18,696,446	7	19,619,005

Table II

Laboratory Animal Science Program Applications - FY 1983

Application Types	Number Rec'd	Amount Requested 1/	Number Appr	Amount Approved 1/	Number Funded	Amount Funded 2/
New.....	38	3,974,767	34	2,632,300	12	809,419
Renewal.....	12	1,748,838	10	1,210,453	6	852,823
Admin Supplement...	2	142,707	2	142,707	2	154,196
Competing Suppl'mt.	-	--	-	--	-	--
Continuation.....	36	4,879,991	36	3,924,699	33	5,185,877
TOTALS	88	10,746,303	82	7,910,159	53	7,002,315

Table III

Laboratory Animal Science Programs - FY 1983

Programs	Number Rec'd	Amount Requested 1/	Number Appr	Amount Approved 1/	Number Funded	Amount Funded 2/
Resource Research..	19	1,601,049	18	1,336,468	10	820,715
Primate Resource...	6	1,366,034	5	896,347	5	1,005,501
Colonies & Models..	9	929,783	9	870,504	7	888,924
Basic Improvement..	11	2,190,471	11	1,343,571	2	229,066
Diagnostic Labs....	17	3,110,220	17	2,272,690	13	2,977,248
Reference.....	5	726,454	4	502,831	3	489,839
Information.....	7	269,617	7	256,895	7	309,593
Research Career....	10	435,103	8	330,267	4	183,726
New Investigator...	4	117,572	3	100,586	2	97,703
TOTALS	88	10,746,303	82	7,910,159	53	7,002,315

1/ Direct Costs
2/ Indirect Costs Included

Table IV

Application Activity and Application Types - FY 1983

Activity and Types	Number Rec'd	Amount Requested 1/	Number Appr	Amount Approved 1/	Number Funded	Amount Funded 2/
P40						
Type 1.....	14	2,646,529	14	1,564,718	3	305,324
Type 2.....	10	1,655,071	8	1,118,186	5	822,376
Type 3.....	1	11,022	1	11,022	1	14,990
Type 5.....	29	4,232,309	29	3,410,786	27	4,747,481
TOTALS	54	8,544,931	52	6,104,712	36	5,890,171
R24						
Type 1.....	9	617,582	8	537,371	3	248,659
Type 2.....	1	25,552	1	25,552	1	30,447
Type 3.....	1	131,685	1	131,685	1	139,206
Type 5.....	6	617,596	6	483,827	5	402,403
TOTALS	17	1,392,415	16	1,178,435	10	820,715
K01						
Type 1.....	10	435,103	8	330,267	4	183,726
Type 2.....	-	--	-	--	-	--
Type 3.....	-	--	-	--	-	--
Type 5.....	-	--	-	--	-	--
TOTALS	10	435,103	8	330,267	4	183,726
R23						
Type 1.....	2	50,986	1	34,000	1	61,710
Type 2.....	-	--	-	--	-	--
Type 3.....	-	--	-	--	-	--
Type 5.....	1	30,086	1	30,086	1	35,993
TOTALS	3	81,072	2	64,086	2	97,703
R13						
Type 1.....	1	47,648	1	38,126	1	10,000
Type 2.....	-	--	-	--	-	--
Type 3.....	-	--	-	--	-	--
Type 5.....	-	--	-	--	-	--
TOTALS	1	47,648	1	38,126	1	10,000
Dual						
Type 1.....	2	176,919	2	127,818	-	--
Type 2.....	1	68,215	1	66,715	-	--
Type 3.....	-	--	-	--	-	--
Type 5.....	-	--	-	--	-	--
TOTALS	3	245,134	3	194,533	-	--
GRAND TOTALS	88	10,746,303	82	7,910,159	53	7,002,315

1/ Direct Costs
2/ Indirect Costs Included

Table V

Training Program Applications - FY 1983

Application Types	Number Rec'd	Amount Requested 1/	Number Appr	Amount Approved 1/	Number Funded	Amount Funded 2/
New.....	4	100,239	3	57,012	1	20,892
Renewal.....	2	208,532	2	177,558	2	161,871
Supplement.....	-	--	-	--	-	--
Continuation.....	10	897,694	10	935,240	10	525,237
TOTALS	16	1,206,465	15	1,169,810	13	708,000

Table VI

Training Programs - FY 1983

Programs	Number Rec'd	Amount Requested 1/	Number Appr	Amount Approved 1/	Number Funded	Amount Funded 2/
NRSA-Institutional.	9	1,014,024	9	1,030,646	9	631,723
NRSA-Individual....	4	82,884	4	82,884	3	62,844
Short Term.....	3	109,557	2	56,280	1	13,433
TOTALS	16	1,206,465	15	1,169,810	13	708,000

Table VII

Contract Program - FY 1983

Programs	Number Rec'd	Amount Requested	Number Appr	Amount Approved	Number Funded	Amount Funded
Primate resource...	2	750,000	2	750,000	2	750,000
Other Program Act..	1	95,000	1	95,000	1	95,000
TOTALS	3	845,000	3	845,000	3	845,000

Table VIII

Small Business Innovative Research Applications - Phase I

Application Types	Number Rec'd	Amount 1/ Requested	Number Appr	Amount 1/ Approved	Number Funded	Amount 2/ Funded
New (RR Primary)...	3	95,559	2	67,931	1	47,283
New (RR Secondary .	4	142,851	2	69,951	-	--
New (RR only).....	6	212,119	3	92,130	-	--
TOTALS	13	450,529	7	230,012	1	47,283

1/ Direct Costs
2/ Indirect Costs Included

Table IX

Summary

Tables	Number Rec'd	Amount 1/ Requested	Number Appr	Amount 1/ Approved	Number Funded	Amount 2/ Funded
I.....	7	19,886,399	7	18,696,446	7	19,619,005
II, III and IV.....	88	10,746,303	82	7,910,159	53	7,002,315
V and VI.....	16	1,206,465	15	1,169,810	13	708,000
VII.....	3	845,000	3	845,000	3	845,000
VIII.....	13	450,529	7	230,012	1	47,283
TOTALS	127	33,134,696	114	28,851,427	7	28,221,603

1/ Direct Costs
2/ Indirect Costs Included

Biomedical Research Support Program
Division of Research Resources

INTRODUCTION

The Biomedical Research Support (BRS) Program, formerly known as the General Research Support Grant Program, was authorized in 1960 by Public Law 86-798 to permit the establishment of "Grants-in-aid to public or nonprofit universities, hospitals, laboratories, and other institutions for the general support of their research and research training programs." The authorizing legislation allows NIH to allocate up to 15 percent of funds appropriated for research grants for such general support to strengthen institutional research in sciences related to health. The Fiscal Year 1983 level was 2.2 percent.

The BRS Program consists of three sub-programs: The Biomedical Research Support Grant (BRSG) Program, the BRS Shared Instrumentation Grant (SIG) Program, and the Minority High School Student Research Apprentice Program (RAP).

PROGRAMS

BIOMEDICAL RESEARCH SUPPORT GRANT PROGRAM

The objective of the BRSG Program is to strengthen and enhance the research environment of institutions heavily engaged in health-related research through the use of flexible funds and local decision-making which enable them to conduct their biomedical research programs more efficiently and effectively. The rationale for the program is to assure that a portion of the total NIH funds for biomedical research involves local decision-making, allowing for appropriate internal balancing of needs as well as early recognition and development of emergent research concepts, techniques, and talent. In addition, there is the need to extend opportunity and responsibility to the scientific administrative leadership at the institutional level to make specific on-site allocations for biomedical research purposes.

In the May 1983 Report of the Ad Hoc Committee on Government Relationships in Support of Science of the Committee on Science, Engineering, and Public Policy, National Academy of Science, entitled "Strengthening the Government-University Partnership in Sciences," the impact of the BRSG was evaluated favorably and the following conclusion was reached:

> The quality of university research would be improved by extending to all federal funding agencies and departments the concept of the Biomedical Research Support Grant of the National Institutes of Health as a means of providing a small amount of general research support. Such support would be allocated most effectively by each university within a general framework established by the government in consultation with the universities and the scientific community.

In Fiscal Year 1982, the program proposed to raise the eligibility threshold from the previous $200,000 to a higher level, to become effective in Fiscal Year 1983. The House and Senate Committees on Appropriations subsequently, in H.R. 97-894 and S. 97-680, requested that the NIH prepare and submit a report on the impact of such a raise on small institutions. The Senate Committee also instructed NIH not to implement the proposed threshold requirements until the requested report had been reviewed as part of the Fiscal Year 1984 appropriation hearings.

In the report submitted to the Appropriations Committees, the NIH noted that the threshold calculations had been devised to meet the original congressional intent that BRSG awards should be "related to the size of the research grants programs of the NIH and of participating institutions... heavily involved in...biomedical research."

The NIH had originally set the eligibility threshold at $100,000 in 1962, had raised it to $200,000 in 1976, and had proposed to raise it to $500,000 in 1983.

In response to the Senate's request, however, the NIH suggested that the threshold be raised to only $350,000 in 1983, to ease the transition to a higher threshold. Such a reduction in the threshold level, noted the NIH, would mean that approximately 40 institutions would lose their BRSG eligibility, including 3 dental schools, 6 pharmacy schools, and 2 nursing schools. Nevertheless, after review of the report submitted by the NIH, both the House and Senate determined that the eligibility threshold should remain at $200,000 for Fiscal Year 1983.

The normal starting date for BRSG awards is April 1 of each year. The NIH portion of the Fiscal Year 1984 appropriations hearings did not occur, however, until mid-April 1983, and the issue was still pending by September 1983. This delay in the resolution of the issue as to the appropriate eligibility threshold level could have delayed the allocation of all BRSG funds until late in 1983. It was recognized that academic institutions count heavily on these awards and on receiving them in a timely fashion. Therefore, procedures were initiated which allowed partial awards, based on the existing $200,000 threshold, to be made on schedule in April 1983. Five hundred thirty institutions qualified at the existing threshold level of $200,000 and received the remaining funds on or about September 7, 1983.

Table I

Distribution of BRSG Awards by Size

Size of BRSG Award*	Number of Grantee Institutions			
	FY 1976	FY 1981	FY 1982	FY 1983
Under $30.0	74	101	114	159
30 - 49.9	87	112	106	86
50 - 99.9	116	115	120	116
100 - 149.9	60	88	67	68
150 - 199.9	48	111	87	36
200 - 249.9	19	--	22	48
250 - 299.9	37	--	--	17
	441	527	516	530
Grant Range	FY 1976	FY 1981	FY 1982	FY 1983
Minimum	$17,418	$12,668	$11,383	$ 9,120
Maximum	261,305	178,699	246,001	282,994
Mean	96,955	84,584	85,311	84,705

*In thousands

Table II

Distribution of BRSG Awards by Type of Institution

Type of Institution	FY 1976	FY 1981	FY 1982	FY 1983
Medicine	106	119	121	120
Dentistry	26	29	31	33
Osteopathy	1	1	2	3
Public Health	12	14	15	13
Pharmacy	13	27	25	23
Veterinary Medicine	10	12	12	13
Nursing	3	5	5	5
Optometry	0	2	2	2
Hospitals	63	62	63	65
Health Departments	2	2	2	2
Research Organizations	71	87	77	86
Other Academic	134	167	161	165
TOTAL	441	527	516	530

ILLUSTRATIVE USES OF BRSG FUNDS

Biomedical research activities that illustrate accomplishments of the program include:

- Pilot research efforts, which test the validity of new ideas and the feasibility of methods to be employed in the research. Pilot research enhances the quality of biomedical research by encouraging innovation, by developing effective research methods, and by selecting the most promising research for project grant applications. It increases research productivity by avoiding false starts, discovering methods that yield quick results, reducing funding risks, and allowing prompt pursuit of new research opportunities. It reduces research costs by discovering efficient research methods and reducing the number of research grant applications to national funding agencies.

- Support of new investigators, including women and minorities, which enhances research quality and productivity by attracting talented persons for biomedical research, introducing new ideas and techniques, and maintaining momentum from training to active research.

- Centrally shared equipment and facilities, which increase research quality by providing sophisticated methods, increasing the available lines of investigation, improving precision of measurements, enabling redirection of research when necessary, and providing expertise for operating complex and specialized resources. The operating expertise increases research productivity by allowing investigators to concentrate on research problems. Centrally shared equipment and facilities also increase research productivity by decreasing the time required to complete research. They reduce research cost by avoiding duplication of equipment, broadening the array of available research techniques so that the most efficient ones can be selected, and decreasing the time required to complete research.

- Interim support and emergency funding, which maintain research quality and productivity by allowing prompt pursuit of new research opportunities, redirection of research, acquisition of research skills, collaboration among investigators, and maintenance of research during temporary interruption of research grant support. These funds reduce the cost of research by eliminating downtime and preventing the loss of personnel, thereby avoiding recruitment and training of new personnel.

The following examples illustrate specific BRSG activities:

A Mechanical Engineering faculty member of a midwestern university proposed exploring the development of a generalized controller for synthesis of walking functions for the locomotor-disabled. The study proposed to aid patients suffering from various forms of lower limb paralysis and in lower limb amputees. Results from the pilot study supported by BRSG funds aided

the investigator in receiving a grant of $450,000 for the first year to continue the project.

A new investigator in the Department of Surgery of an eastern hospital received BRSG funds to initiate studies on the effect of angina pectoris drug therapy on gallbladder function. One of the drugs used to treat angina pectoris sometimes causes stomach discomfort, and it was surmised that this side effect was actually an effect of the drug on gallbladder activity. The investigator used the BRSG funds to establish a model system for the effect. He obtained sufficient preliminary data to support his hypothesis and to apply to national agencies for support to continue the project. Thus, BRSG funds have allowed a new clinician to establish a research project and become an active participant in biomedical research.

BRSG funds were used as seed money to support a research effort by an investigator in a hospital on the East Coast. The investigator was able to establish an artificial blood vessel in a culture dish. Using this system, the investigator noted the effect of a drug on differentiation of primitive cells into new types of cells (muscle, fat, and cartilage cells). This has opened up a new research effort on cell differentiation.

An established faculty member in a Department of Chemistry of an eastern university received BRSG funds to initiate a pilot research project on protein structure. The investigator revised the old model for how hemoglobin delivers oxygen to the tissue. The scientist also has received two awards as well as NIH support to continue the research.

At a western medical school, BRSG funds were awarded to a new clinical faculty member to initiate a pilot project combining both basic and clinical research on rheumatoid arthritis. As a result of the preliminary data supporting the involvement of a rheumatoid factor and antibody complex in the pathogenesis of the disease, the investigator was able to gain support for his project by the NIH for several years.

During a funding hiatus, an associate professor in a northwestern medical school needed funds to sustain a laboratory research program on tumor viruses and genital herpes in the laboratory. A lapse occurred between the time one grant period ended and the time the revised grant started. A BRSG grant allowed the investigator to maintain personnel during the period and keep the research program operating. As a result of new data collected, institute funding was obtained to continue the research.

SHARED INSTRUMENTATION GRANT (SIG) PROGRAM

As part of its mission to create, develop, and maintain research resources needed by NIH-supported biomedical investigators throughout the nation, the BRSG program continued its competitive shared instrumentation grant program initiated in Fiscal Year 1982. The program was established in recognition of the long-standing need in the biomedical research community to cope with rapid technological advances in instrumentation and the rapid rate of

obsolescence of existing equipment. The objective of the program is to make available to institutions with a high concentration of NIH extramural research awards research instruments which can only be justified on a shared-use basis and for which meritorious research projects are described.

This program is designed to meet the special problems of acquisition and updating of expensive shared-use instruments which are not generally available through other NIH mechanisms. The BRSG Shared Instrumentation Program is intended for a broad community of NIH-supported investigators.

In Fiscal Year 1983, 160 applications, requesting $30.4 million, were reviewed. The list of requested instruments included cell sorters, an image analysis and graphics system, electron microscopes, mass spectrometers, NMRs and protein sequencers and analyzers, and other highly sophisticated instruments. Of these requests, 91 awards were funded with a total budget of $14.0 million.

Image analysis equipment acquired through a Fiscal Year 1982 Shared Instrumentation Grant to the Washington University School of Medicine in St. Louis, Missouri, became operational during 1983. It is serving as the cornerstone of the new Laboratory of Neuro Imaging, Department of Neurology and Neurological Surgery, at the McDonnell Center for the Study of Higher Brain Functions. Computer-assisted image processing is providing neuroscientists with analytical instrumentation that reduces the ambiguity of visual data by converting it to high-resolution quantitative images. An investigator can explore and analyze the numerical images more quickly and completely than was previously possible.

Table III

DRR/BRS Shared Instrumentation Grant Program
Application and Award Data
for FY 1982 and FY 1983
By Type of Instrument

Instrument Type	No. of Applications 1982	No. of Awards 1982	No. of Applications 1983	No. of Awards 1983
Acoustic Microscope	1	-	-	-
Cell Sorter	38	4	19	12
Image Analysis/Graphics	18	2	13	6
Diffractometer	5	-	6	5
Electron Microscope	46	6	45	24
EPR	3	2	1	1
ESR	2	-	1	-
Fermentor	2	1	2	1
HPLC	3	-	-	-
Mass Spectrometer	25	2	26	14
NMR	28	2	13	8
Optics	-	-	1	1
Other Spectrometers	7	1	9	5
Protein Seq./Analyzer	24	2	21	12
Radiology	2	1	2	2
X-Ray	1	-	1	-
Total Applications	205	23	160	91

Table IV
DRR/BRS Shared Instrumentation Grant Program
Application and Award Data
for FY 1982 and FY 1983
By Type of Institution

Type of Institution	No. of Applications 1982	No. of Awards 1982	No. of Applications 1983	No. of Awards 1983
Academic	65	7	59	37
Dentistry	9	-	6	3
Hospital	16	2	7	6
Medicine	74	11	59	35
Optometry	1	-	1	1
Osteopathy	1	-	0	0
Pharmacy	11	-	6	1
Public Health	5	-	5	1
Research Org.	20	3	15	6
Vet. Medicine	3	-	2	1
Totals	205	23	160	91

Table V

DRR/BRS Shared Instrumentation Grant Program
NIH Major User Data for FY 1982 and FY 1983
By NIH-Funded Research Grant of User

Awarded Applications		Major Users	NIH-Funded Research Grants of Users											
			CA	AI	DE	ES	AM	GM	HL	HD	AG	NS	EY	NIH
FY 1982	23	212	74	30	6	3	40	47	30	24	3	24	6	287
FY 1983	91	782	205	86	43	25	126	227	118	54	15	80	41	1,020

MINORITY HIGH SCHOOL STUDENT RESEARCH APPRENTICE PROGRAM

The purpose of the apprentice program is to provide meaningful experience in various aspects of health-related research in the expectation that some of the apprentices will decide to pursue careers in research related to health. Direct support to the apprentice is as salary; stipends are not allowed.

Eligible institutions are those that were awarded grants during the latest complete Federal fiscal year from either the Biomedical Research Support Grant (BRSG) Program or the Minority Biomedical Research Support (MBRS) Program, both of which are administered by DRR, NIH. Only one application for the program is submitted by the recipient of both the BRSG and MBRS awards. Support is provided at a level of $1,500 for each apprentice position allocated. A total of 277 institutions received awards for Fiscal Year 1983, supporting a total of 666 students.

A recent review of annual progress reports received from the individual institutional program directors reveals that students have been exposed to laboratory assignments and tasks for the development of scientific information, research skills, and possible interest in research careers. Experiences varied from laboratory to laboratory, but most students were assigned research problems, collected data, and organized and reported their findings in written papers and seminars. Students and faculty largely described the experience as rewarding and challenging for the apprentices. All the program directors who commented on the performance of the program were positive, with most considering it quite successful. The exposure was also a way for many apprentices to gain an early awareness of the conditions of college life and for some to work with college students on projects. Mentor relationships established with graduates and undergraduates were felt to be valuable. Although a few students reacted negatively to the experience, most found scientific research an attractive career opportunity.

Biotechnology Resources Program
Division of Research Resources

INTRODUCTION

The Biotechnology Resources Program (BRP) was initiated in 1962 after Congress expressed interest in the establishment by NIH of an activity focused on specialized equipment needed for biomedical research. Since that time, the BRP (formerly called Special Research Resources) has modified and expanded its scope. In the early years, the program mainly supported large general-purpose computer centers in medical schools. It later moved into an extremely broad and innovative array of biomedical technologies. The program now places greater emphasis on regional and national sharing of resources. Today, the program focuses on applications of knowledge engineering, information technology, biomedical engineering and digital technology for biomedical and clinical research programs, and technologies for the study of biomolecular and cellular structure and function.

RESEARCH ACCOMPLISHMENTS

USE OF COMPUTERS TO RESTORE NEUROLOGICAL FUNCTION

The Rockefeller University Microprocessor Biotechnology Resource is collaborating with the Department of Orthopedics and Rehabilitation of the University of Miami School of Medicine in an exciting new method, using biofeedback, to treat the effects of brain damage and injuries to the spinal cord that occur during pregnancy or at birth. Such defects and injuries may interfere with the patient's ability to walk and to feed himself or herself and, in some cases, may produce uncontrollable changes in blood pressure with changes in posture. With the help of the Rockefeller University Resource, the University of Miami School of Medicine has developed a training program for such patients using microcomputer-based instruments to detect muscle potentials from affected sites and to display the results in visual and auditory signals. Patients can use these signals to learn to walk, to grasp, and to control blood pressure. Dramatic instances of rehabilitation have already been demonstrated, particularly in children diagnosed as having cerebral palsy (CP) of the spastic type, caused by trauma during pregnancy or birth. In particular, several 11- to 13-year-old children with CP who were given physical therapy continuously after diagnosis and who remained with non-functioning hands, were treated with physiological feedback. Computer-processed signals from four muscle groups were typically used as visual feedback. After approximately eight 45-minute sessions during a 4-week period, all of the treated children had functioning hands, i.e., they were for the first time capable of grasping objects, dressing themselves, handling utensils, and feeding themselves. In total, 8 children were treated in this way with 100 percent success.

Future work at this resource will include the development of portable and lightweight devices through very large scale integrated circuit technology to promote and disseminate these revolutionary new techniques.

DEVELOPMENT OF NEW IMAGE RECONSTRUCTION TECHNIQUES FOR SUPERIOR 3-D IMAGING OF MOVING ORGANS, PARTICULARLY THE HEART

A new computer program has been developed at the computer resource at the Mayo Foundation. The program produces images of the heart superior to those produced by the techniques commonly used in X-ray computer tomography (CT) scanners. The new technique takes advantage of the scanning geometry and timing of X-ray CT machines to obtain information from subsequent points in time to aid in the production of the image at a previous point in time. The result is a higher-resolution image with less artifact than that obtained if only the data at a given point in time are used. This scheme is readily adaptable to current X-ray CT systems and should provide improved images of moving organs without an increase in X-ray dose. Motion of organs, particularly the heart, frequently causes blurring and streaks in conventional CT scans. The new algorithm will produce sharp images for short time intervals, during the heartbeat, for example, so that accurate measurements of dynamic organ structure and function can be carried out.

THIN LINEAR THERMOMETER ARRAYS FOR TEMPERATURE MEASUREMENT DURING LOCALIZED CANCER HYPERTHERMIA

Hyperthermia of cancerous tissue has been shown by several investigators to produce shrinkage of tumors when used as the sole treatment method and when used in conjunction with either chemotherapy or ionizing radiation. Hyperthermia is accomplished using ultrasound or electromagnetic radiation for deep heating of tissues. One of the basic problems in hyperthermia is determining the amount and extent of temperature rise in tissue. Great variations in tissue structure and blood flow occur from individual to individual, at different body locations within the same individual, and at the same body location in an individual over the course of time. As a result, identical treatment regimens with a given heating apparatus can produce highly variable temperature profiles and unrepeatable results.

Successful use of hyperthermia in a clinical setting will require feedback, in the form of temperature measurement, at several points within the tumor and in the tissue surrounding the tumor. Ideally, such temperature measurement should be non-invasive, so that no disturbance of tissue occurs because of the temperature measurement. In practice, a minimal amount of tissue invasion is necessary if temperature is to be measured at several localized interior points. At a minimum, a single puncture wound is necessary. Several "thermometer points" located along the length of such a puncture offer a practical optimum.

The National Resource for Silicon Biomedical Sensors in the Stanford University Integrated Circuits Laboratory, in collaboration with the hyperthermia research team in the Department of Radiology at the Stanford

University Medical Center, has developed a miniature linear thermometer array, composed of silicon diodes on a flexible substrate, which will provide a near-optimal means of temperature measurement during localized heating (hyperthermia) used to treat cancer. The thermometer array can be calibrated to give absolute temperature at 20 points within the body, to an accuracy of 0.2^{o} (Celsius) over a typical range of temperatures encountered during hyperthermia (37^{o}-45^{o} Celsius).

THE PHYSICAL MAPPING OF DNA

Genetic information is encoded in DNA molecules, which consist of long sequences of simple nitrogen-containing bases chained together and paired ("base pairs") to form the famous double helix. The relative positions of genes in a DNA molecule are expressed by a genetic map of the chromosome. A physical map of DNA differs in that properties of the molecule are related to positions along its length between sites having a community of interest, such as vulnerability to specific "restriction enzymes" which break the molecule at particular base-pair sequences. The most complex DNA sequences that have been completely mapped with any restriction enzyme are the chloroplasts of lower plants, for which the DNA consists of only 150,000 base pairs.

Scientists at the Washington University Resource for Biomedical Computing are collaborating with the Department of Genetics to develop a unique, global approach which makes feasible the restriction mapping of much more complex DNA. The ultimate objective is to develop techniques which could be applied to man and other mammals, the DNAs of which contain about 5 billion base pairs. The global approach to physical mapping uses partial digestion with restriction enzymes to create large DNA fragments which are then cloned, using recombinant techniques. The pools of cloned fragments are then digested further with enzymes, and the resulting sub-fragment sizes are identified by means of gel electrophoresis. Digital computing techniques will be used to process the large amount of experimental data to deduce the complete physical map. A model of DNA base-pair sequences has been developed which is consistent with experimental observations and which has served to guide the selection of restriction enzymes best suited to the task. The model has demonstrated the value of both order and base-pair-length information and has thereby proved useful to experimental protocol development. A computer-based system also is under construction for semi-automated gel analysis to achieve accurate fragment sizing. In contrast to other methods, the global approach being developed at the Washington University resource could be applied to DNA of any arbitrary complexity.

MODELING OF COLICIN E1

The functioning of ion channels is essential for the conduction of signals in all nerve cells. Computer model building is being carried out at the Columbia University Computer Resource on Colicin E1, a bacterial protein which produces an ion channel in an artificial lipid membrane. This protein can kill sensitive bacteria by making a hole in their cell membrane. The total sequence of the protein is 522 amino acid units. Workers at the Columbia resource have isolated a sub-fragment of 152 amino acids which has the full channel-forming activity of the intact protein.

Using the facilities of the computer resource at Columbia University, scientists have generated models of plausible molecular structures which satisfy all of the constraints dictated by the physical chemistry of the system. The model makes very explicit predictions as to the effect of various mutations in the structural gene which codes for the colicin protein. Six altered proteins have been made and tested at the Columbia resource, all of which give results consistent with at least one of the computer-generated models.

The colicin system is unique in that it is the only peptide which spontaneously forms an ion channel, has a structure which can be defined at the level of the arrangement of its atoms, and has a structural gene accessible for in vitro modification. Further studies of ion channel function with both bacterial and brain proteins will require the use of a new special-purpose super-computer, which has been designed at the Columbia facility, but which has not yet been constructed.

RHEUMATOLOGY CONSULTATION SYSTEM

The Rutgers University resource is developing an expert system in rheumatology in collaboration with clinical investigators at the University of Missouri. The rheumatology consultation system produces accurate diagnoses on problems within its scope of expertise. At more than 1,000 rules, it is the largest expert system to have been transferred to a microcomputer. The diagnostic model has been expanded from 7 to 26 rheumatic diseases and is expected to expand to a capacity of 35 or 40 diseases. The case library has about 400 cases. Because of its size and complexity, developing treatment plans in this area should prove a challenge that may lead to reconsiderations of the models used in other applications. The knowledge gained should serve knowledge engineering applications in other disease areas.

EARLY DIAGNOSIS OF LEPROSY

An investigator at Colorado State University collaborated with the resource staff at the University of Colorado School of Medicine in using mass spectrometry to establish the structure of a specific antigen for the leprosy bacillus. The research may lead to a simple test for leprosy, and the National Institute of Allergy and Infectious Diseases is sponsoring further research. The scientist will be supplying the glycolipid antigen for serological tests in connection with a Cooperative US/India Program for Leprosy Research.

SECONDARY ION MASS SPECTROMETRY WITH CESIUM ION PRIMARY BEAM

Fast atom bombardment mass spectrometry has been widely explored as an approach to analysis of biological compounds with molecular weights in the

oligopeptide-to-small-protein range. The method is based upon the use of a neutral primary beam (xenon atoms) to bombard the sample. Recently, two investigators at the mass spectrometry resource, University of California, San Francisco, explored the possibility of replacing the neutral primary beam with an alkali ion beam. This would have great advantages in focusing and gun design. A cesium ion gun was constructed and used to evaluate whether an ionic primary beam could be used effectively with a liquid matrix target. The approach yielded both better sensitivity and a relative reduction in fragments produced when compared to similar studies with a xenon source. Studies on the use of the method with mass resolutions up to approximately 10,000 are continuing.

MOLECULAR WEIGHT MEASUREMENTS

The electron microscope facility at Brookhaven National Laboratory (BNL) has been using the scanning transmission electron microscope to determine molecular weights of single particles and mass per unit length of polymers. Accurate molecular weights often permit the elucidation of structural organization, and several collaborators are exploring the use of this special capability to study a variety of biological problems. Microscope accuracy is about 4 percent at 100,000 daltons and 1 percent or better above 10^6 daltons on a single particle, so the method is probably the most accurate available for molecules of 300,000 and up. Studies of viruses, muscle filaments, proteins, nucleic acids, cellular particles, and catalysts have been carried out during the past year. The BNL STEM is the only U.S. microscope capable of measuring biological mass accurately.

MICRO-RESONATOR FOR ELECTRON SPIN RESONANCE

In all types of analytical instrumentation, it is important to be able to measure very small samples. Electron spin resonance (ESR) spectroscopy is no exception, and scientists at the National Biomedical ESR Center have developed a new type of microwave-resonant sample structure that is unusually small. For X-band, the usual microwave frequency at which ESR measurements are made, the new resonator can be as small as a cylinder 1 mm in diameter and 2.5 mm long. Typical volumes of aqueous samples used with this resonator are less than 1 uL, as compared to the usual sample volume of 100 uL. The quality of the spectra obtained is at least similar and often better with the new resonator, and this advance will expand the biological and biochemical usefulness of the technique.

X-RAY ABSORPTION SPECTROSCOPY

Investigators at the Stanford University Synchrotron Radiation Biotechnology Resource have built and evaluated an energy-dispersive spectrometer for the rapid measurement of X-ray absorption spectra using synchrotron radiation. The system, which uses a dispersive geometry and a position-sensitive detector to record the complete spectrum simultaneously, has yielded useful spectra in less than 0.1 second. The system could prove effective for use in dynamic structural studies of biological systems.

WORKSHOPS AND CONFERENCES

APPLICATIONS OF FLOW CYTOMETRY TO GENE MAPPING

An international conference on applications of flow cytometry to gene mapping and chromosome analysis was held in Santa Fe and Los Alamos, New Mexico, in October 1983. The BRP and the Department of Energy acted as sponsors. The conference was a forum both for the dissemination of current flow cytometric capabilities and the formulation of new approaches to problems in the genetics of eucaryotes.

MEASUREMENT AND CONTROL OF FLOW WITH APPLICATIONS TO PHYSIOLOGICAL SYSTEMS

Attendees at a workshop on March 14-17, 1983, in Monterey, California, received an overview of the state-of-the-art methods for flow measurement and control, and discussed problem areas in biomedical instrumentation. Topics discussed included methods of flow measurement (NMR, ultra-sound, electro-magnetic, etc.); flow control devices (pumps, valves, shunts, restrictors, etc.); and applications to blood flow, air flow, and other flow systems (dialysis, cerebrospinal, urinary, etc.).

PROPHET COLLOQUIUM

The 11th Annual PROPHET Users' Colloquium was held at Airlie, Virginia, June 7-9, 1983. Approximately 100 biomedical scientists from academia, industry, and Federal agencies participated. Among the academic participants were scientists supported by the Minority Biomedical Research Support Program, the Primate Research Centers Program, and the General Clinical Research Centers Program.

A major scientific presentation was made by PROPHET user Dr. Elvin Kabat of Columbia University and the NIH who spoke on "Antibody Combining Sites." Other scientific presentations by PROPHET users included "Investigation of the Legionnaires Disease Outbreak Using PROPHET" and "Quantitative Determination of Dopamine Receptor Subtypes." Dr. Christine Carrico of the National Institute of General Medical Sciences spoke on "An Introduction to GenBank, the Genetic Sequence Data Bank," a data bank which utilizes the PROPHET system.

Fourteen workshops were held, in two series, so that each colloquium participant could take part in a total of four workshops, two from each series. Workshop topics included "Using the PROPHET Interface to the Cambridge Crystallographic Data Base," "Biological Sequence Data Handling in PROPHET," "Using the MM2 Model Builder with PROPHET Molecules," and "Stat/Math Methodologies."

ARTIFICIAL INTELLIGENCE IN MEDICINE

A workshop on artificial intelligence in medicine was held in Baltimore, Maryland, October 26-27, 1983. The workshop participants considered methods to accelerate the automatic acquisition of knowledge, transfer of existing systems to a finished product, representation of large knowledge bases, and influence of new hardware on research in this area.

PROGRAM DEVELOPMENTS

SMALL BUSINESS INNOVATION RESEARCH PROGRAM

Public Law 97-219, an amendment to the Small Business Act, requires the agencies of the Public Health Service and certain other Federal agencies to set aside a specified amount of their research and development budgets for a Small Business Innovation Research (SBIR) Program. The purpose of this legislation is to stimulate technological innovation, use small business to meet Federal research and development needs, increase private-sector commercialization of innovations derived from Federal research and development, and foster and encourage participation by minority and disadvantaged persons in technological innovation.

The SBIR Program will consist of three phases. The BRP has awarded three grants under the first phase of this program. Grants which have been awarded are: (1) a grant to develop high-technology computerized instruction packages for use in basic science training in medical schools; (2) a grant to determine the viability of a new memory storage technique called Photon Echo Memory; and (3) a grant to develop a fiber optic pressure and temperature sensor for intravascular measurements.

NEW GRANTS AWARDED

The program funded nine new resource grants this year. A resource for mathematical modeling, digital computation, and simulation of the incidence and propagation of disease was funded at the University of Minnesota. The resource will concentrate on infectious disease, including epidemics and vaccination; chronic disease, including intervention and prevention strategies for populations; and genetics and inherited disease.

A resource devoted to the computer analysis of images derived from autoradiography originating from the radiations of 2-deoxyglucose was funded at Drexel University. An important aim of the resource will be an investigation of system requirements of a computer-based autoradiography system that will be sufficiently inexpensive so that it can be used in individual investigator laboratories.

A biomedical simulation resource at Duke University also was funded. The principal objective of the resource is to make simulation capabilities more readily available to the biomedical research community by simplifying the necessary computer procedures and providing access to a computer optimized for simulations, particularly those requiring large amounts of computation.

An Electron Spectroscopy for Chemical Analysis (ESCA) resource for the study of biomaterials was funded at the University of Washington, Seattle. The principal investigator plans an aggressive core and user research program on

applications of ESCA to biomaterial surfaces, surface energy analysis, and the nature of the interactions between biological components and synthetic materials.

A National Center for Biomedical Infrared Spectroscopy has been funded at Battelle's Columbus Division, Columbus, Ohio. Research topics will include solution studies of proteins, blood interactions with synthetic materials, and studies of RNA directly in cells.

The San Francisco Laser Center, a regional laser lending facility supported by the National Science Foundation, has broadened and expanded its user activities in the biomedical research area with the support of the BRP. A resource has been funded at the University of California, Berkeley, to provide equipment and expertise to the biomedical community. Core research projects at Berkeley and at Stanford University are designed to expand the usefulness of laser technologies to biochemists and cell biologists.

An investigator at the University of California, San Diego, has been developing, with NIH support, a "fly's eye" system for using multi-wire detectors to collect protein crystallographic X-ray data. The system was tested in the spring, and a resource now has been established to make the data collection capabilities of this system widely available. The BRP supports a second X-ray data collection resource, based on a large single multi-wire detector, at the University of Virginia.

A third resource in the area of biological applications of synchrotron radiation has been funded at the Cornell CHESS facility. The resource is to emphasize wide-angle protein crystallography studies.

Two new resource-related research projects were funded this year. A resource-related research project in clinical decision-making and artificial intelligence was funded at the Massachusetts Institute of Technology. The project will focus on clinical cognition, the expert program "digitalis adviser," and further development of the program which will allow clinicians to build "decision trees."

A resource-related research project to extend the capabilities of a computer-based consultation system in cancer chemotherapy (ONCOCIN) was funded at Stanford University. One aim of the project is to test ONCOCIN at a practice site of a community-based oncologist. Another aim is to develop and test methods for evaluating the impact of the ONCOCIN system on the mode of practice of physician users.

Fourteen small grants were funded from the first round of proposals received. These grants cover a wide range of new, high-risk technologies. Included are a grant to develop a microelectronic device to measure, percutaneously, inert gas concentration in blood, at levels of concentration which are at the limit of present-day technology; a grant to develop a theoretical model for a single-drop electrostatic generator, which would permit synchronous cell

sorting and which if fitted to existing cell sorters should increase speed by a factor of two or more; and a grant to develop a two-dimensional area detector using charge-coupled arrays for use in electron diffraction studies of crystals.

ADMINISTRATIVE ISSUES

The Division of Research Grants established a Biomedical Engineering and Technology (BET) flexible study section. The BET consists of two subgroups, BET-1 and BET-2. BET-1 will review applications in computer technology and biomedical engineering; BET-2 will review applications in analytical chemistry, including mass spectrometry and surface elemental microanalyses. Ad hoc members will be used. The committee will review the full spectrum of activities: regular research applications, BRP applications, program projects, center applications, and other specialized applications. Applications were assigned to BET beginning June 1, 1983. The Division of Research Grants (DRG) houses the executive secretary of BET. Special study sections in DRG will review those BRP applications in scientific and technological areas not covered by BET.

An ad hoc committee was convened on February 28 and March 1, 1983, to review the concept of the PROPHET computer resource. PROPHET is funded through a contract to Bolt, Beranek and Newman, Inc. PROPHET is a computer-based information handling system with special emphasis on capabilities in mathematical modeling, molecular modeling and manipulation techniques, and data management capabilities tailored to the needs of the individual laboratory scientist. PROPHET was found to be successful as a pioneering effort in providing major computing power to research scientists and in its responsiveness to user needs and opportunities for creative research. The ad hoc review group recommended the establishment of an advisory committee for PROPHET to counsel DRR on future directions for the system. The first meeting of this committee, on October 18-19, 1983, provided a general introduction to the PROPHET resource, and included information from PROPHET users and a review of long-term and short-term priorities.

FUTURE DIRECTIONS

NUCLEAR MAGNETIC RESONANCE

Following the recommendations of a nuclear magnetic resonance (NMR) task force meeting on May 9, 1983, and the Biotechnology Resources Review Committee, BRP issued an announcement in the October 14, 1983, NIH Guide to Grants and Contracts, inviting resource grant applications in areas of in vivo NMR spectroscopy and NMR imaging with emphasis on imaging with nuclei other than hydrogen, such as phosphorus, sodium, fluorine, and carbon.

TRAINING

A June 4, 1983, panel discussed training needs in computer science for biomedical researchers. The consensus was that training programs in computer science and other types of advanced technology were needed. The panel also believed that consideration should be given to both individual fellowships and training grants to institutions. In addition, members recommended that some provision should be made to allow for short-term training programs, from several weeks to four months, to permit training in a particular technique.

The Biotechnology Resources Review Committee considered the panel's report at its meeting on July 21, 1983. The committee recommended that BRP consider wider and better-defined training within biotechnology resources. The training issue was discussed at a meeting of principal investigators of biotechnology resources on November 14-15, 1983.

USE OF BIOTECHNOLOGY RESOURCES

One of the primary measures of BRP's accomplishments is the extent to which its sponsored resources assist the various NIH categorical programs. With their highly skilled staff scientists and their specialized and often unique facilities, biotechnology resources are frequently the scenes of productive encounters among experts in certain technologies and experts in certain biomedical disciplines. Table I lists the PHS grants that made use of biotechnology resources and notes the dollar amounts of these grants. The distribution of research assisted by the BRP reflects in part apportionment of research funds to the NIH institutes and other agencies.

The total number of projects in biotechnology resources and the number of investigators who made use of biotechnology resources are given in Table II for Fiscal Years 1980, 1981, 1982, and 1983. The number of publications resulting from research projects conducted in biotechnology resources in these years is also given in Table II.

EXPENDITURES BY CATEGORY

During Fiscal Year 1983, the program supported resource grants, resource-related research project grants, new investigator research awards, conference grants, small grants, SBIR grants, and contracts. The technologies provided by the biotechnology resources are classified as follows:

Type	Number	Awarded FY 1983
Knowledge Engineering and Information Technology		
Knowledge Engineering	8	$4,339,844
Information Technology	10	$3,190,961

Type	Number	Awarded FY 1983
Biomedical Engineering and Digital Technology		
Biomedical Engineering	9	$1,750,257
Digital Technology	6	$2,282,793
Technologies for Study of Biomolecular and Cellular Structure and Function		
Biomolecular Structure and Function	32	$8,944,071
Cellular Structure and Function	13	$2,952,033

The aggregate annual level for the grant and contract activities is approximately $23.5 million.

TABLE I

PHS Support for Investigators
Using Biotechnology Resources for FY 1983

NIH Institutes	Number of Grants	Awarded Dollars*
Aging	6	898
Allergy and Infectious Diseases	41	3,948
Diabetes, Digestive Diseases and Kidney	101	10,587
Cancer	103	11,939
Child Health and Human Development	29	4,457
Dental Research	6	652
Environmental Health Sciences	14	798
Eye	35	4,024
General Medical Sciences	229	26,176
Heart, Lung and Blood	121	19,957
National Library of Medicine	8	869
Neurological and Communicative Disorders and Stroke	60	5,503
Fogarty International Center	4	52
Division of Research Resources	43	7,826
Total NIH	800	97,686
Other PHS Components		
Alcohol, Drug Abuse and Mental Health Administration	27	2,018
Health Resources Administration	3	350
Centers for Disease Control	-	-
Food and Drug Administration	-	-
Office of Health Research, Statistics and Technology	3	498
Total PHS	833	100,552

*In thousands

TABLE II

Use and Publication Records of Biotechnology Resources

	FY 1980	FY 1981	FY 1982	FY 1983
No. of Projects	1,421	1,346	1,938	2,113
No. of Investigators	2,088	2,180	3,104	3,672
No. of Publications	1,182	1,146	2,115	2,505

General Clinical Research Centers Program
Division of Research Resources

INTRODUCTION

MISSION

The General Clinical Research Centers (GCRC) Program provides resources for 75 General Clinical Research Centers where highly qualified investigators have the opportunity to advance the knowledge of medicine in a clinical setting. The program was conceived in 1959 when the United States Senate determined the need for increased patient-oriented research. In the interval between the initial center grant award in 1960 and Fiscal Year 1983, the program has gained and maintained a dynamic cadre of clinical investigators. Specific goals of centers funded by the program are:

- To learn more about normal and abnormal body function and about the cause, progression, prevention, control, and cure of human diseases
- To provide an optimal setting for controlled investigation by clinical scientists supported by the NIH and other organizations
- To encourage increased collaboration among investigators in the basic and clinical sciences
- To encourage, develop, and maintain a national corps of expert clinical investigators
- To provide resources that allow advances in basic scientific knowledge to be translated into methods for improved patient care.

GENERAL DESCRIPTION OF PROGRAM AND EVOLUTIONARY TRENDS

Conducting a successful clinical research protocol is highly dependent on the research setting. Thus, the centers are designed to provide the best possible environment, including the personnel and technical tools, in which researchers can provide superior care for research patients while acquiring new health knowledge.

The research capacity of the 75 centers in the GCRC Program is equivalent to that of a single 600-bed hospital devoted entirely to human studies. The centers accommodate both inpatients and outpatients, providing the specialized care needed for studies on both adult and children. Currently, 88 beds are on pediatric wards or in children's hospitals. Of the 75 centers, 66 admit pediatric patients on a regular basis. One center is devoted to research on maternal and fetal problems surrounding delivery; another is devoted to research involving premature infants. One center is entirely involved in outpatient research.

During the 23 years of the program's operation, there has been an increase in the efficiency of use of the research beds; fewer beds are supported, the duration of inpatient stay is shorter, and the production of scientific publications is higher. A considerable share of the research is now conducted on outpatients, and one center is entirely an outpatient facility. The cost to operate the centers, which were formerly supported entirely by the program, is now supplemented by reimbursement for routine cost and treatment of one-third of the research patients by third-party carriers. In the past 7-8 years, the program has introduced the Clinical Associate Physician Program to support newly independent clinical investigators with nearly 100 graduates. The well-accepted and highly successful trademarked CLINFO System for computerized handling of clinical research data is now supported in more than 20 centers. Core laboratories continue to be an integral part of the resources supported, and in some, sophisticated equipment such as mass spectrometers has been acquired. Finally, efforts have increased in recent years to provide a formal evaluation of the contributions of the program to specific advances in medicine.

TYPICAL CENTER

A "typical" clinical research center can accommodate both inpatients and outpatients and supports 1 or 2 medical program directors, 12 nurses, 3 dietitians, 2 laboratory technicians, and administrative personnel. The budget for a typical research center is shown in Table I.

Most centers contain approximately 8 beds (range, 4 to 30). Centers also contain treatment rooms, a core laboratory, a diet kitchen, patients' lounge space, a nurses' station, a conference room, and outpatient space. The number of centers, patient days, and outpatient visits is shown in Table II. The program budget in real and constant dollars is shown in Figure I. The GCRC Program pays the hospital costs of all patients admitted to the centers solely for research purposes. About 35 percent of patients participating in research projects require hospitalization for diagnosis or treatment; these patients are billed for this portion of their stay, usually through third-party insurers.

When routine tests are required for patients at a clinical research center, the hospital's clinical laboratory often handles them. Because standard hospital laboratories are not always able to provide routine tests and assays with the degree of speed or accuracy needed by clinical investigators, these are provided by the core laboratory. The kinds of tests performed by core laboratories vary from center to center, depending on the requirements for core services.

The metabolic kitchen is another part of a center essential for maintaining its controlled environment. It provides a level of dietary control not available elsewhere in the hospital.

One of the most important elements of the center is the group of highly trained paramedical personnel. Nurses, dietitians, laboratory workers, and other support personnel, trained in the methodology of clinical research, perform duties essential to maintaining high clinical research standards.

CLINFO

The CLINFO system is a computer-based data management system designed for clinical investigators. The prototype was tested by clinical investigators in 1977 and found to be useful for managing and rapidly analyzing data. The GCRC Program subsequently has awarded 22 production versions of CLINFO to the GCRCs, as shown in Table III. The CLINFO system has been accepted with much enthusiasm, and several additional GCRCs are applying for the system.

The GCRC Program is collecting more specific evaluation data on the extant CLINFO systems through annual reports that the centers submitted to the GCRC Branch. The 17 CLINFO sites reporting this past year have used a total of 56,247 connect hours; the more mature systems exceeded 6,000 connect hours each. CLINFO has been used in the preparation of 453 GCRC publications and 315 abstracts in the past year. The present cost to the GCRC Program for the 22 awarded CLINFO systems is $2,032,119. The incremental costs to the program from 1978 on can be noted in Table IV.

The system managers continue to be an integral part of the CLINFO system. The third meeting of the Organization of the CLINFO System Managers (OCSM) was held at the National Institutes of Health on October 27-30, 1982. The organization's charter provided data for management assistance to investigators and to the maintenance and enhancement of the centers with CLINFO in a manner designed to increase medical knowledge. The CLINFO utilization report form, which was developed with the OCSM, was used in the Fiscal Year 1982 Annual Report. The next meeting of the OCSM was held in early November 1983.

During Fiscal Year 1983, new guidelines were adopted for applications for the CLINFO system. One section which received particular attention was the characterization of the qualifications of the system manager. The system manager is selected by each institution according to the new guidelines and is confirmed after a review of qualifications by program staff.

CLINICAL ASSOCIATE PHYSICIAN PROGRAM

Clinical research activities supported by the categorical institutes of the NIH and other organizations are dependent on a corps of well-trained clinical investigators. A serious decline in the number of young physicians entering biomedical research careers during the mid-1970s and a decrease in the support of sub-specialty fellowship training prompted the GCRC Program to initiate the Clinical Associate Physician (CAP) Program. The program, which provides post-fellowship salary support, is designed to support young medical

scientists at the beginning of their careers in clinical investigation. Of the 97 individuals who have completed the program, approximately 84 percent have remained in academic medicine. To date, half of those still in academic medicine have obtained NIH support for their research.

HONORS AND AWARDS

Dr. Gregory Mundy, Program Director of the GCRC at the University of Texas, San Antonio, was the 1982 recipient of the Fuller Albright Award of the American Society for Bone and Mineral Research. The award, given at the society's annual meeting in June, honors an outstanding investigator under the age of 40.

Dr. Arthur Atkinson, Professor of Medicine and Pharmacology and Program Director of the GCRC at the School of Medicine at Northwestern University, received the Rawls-Palmer Award at the meeting of the American Society for Clinical Pharmacology and Therapeutics. This award is given annually to a clinical pharmacologist for significant contributions to drug investigation which apply the effects of modern drug research to the care of patients.

Dr. Charles Y.C. Pak, Program Director of the GCRC at the University of Texas (Southwestern) Medical School, has been appointed Donald W. Seldin Professor of Clinical Investigation. Dr. Pak delivered an invited "state-of-the-art" address on renal stones at the 1982 meeting of the American Urological Association.

Dr. Mortimer G. Rosen, Director and Professor of the Department of Obstetrics and Gynecology and Program Director of the Perinatal General Clinical Research Center at Cleveland Metropolitan General Hospital (Case Western Reserve University), received the Solomon A. Berson Medical Achievement Award in the Clinical Sciences from the New York University School of Medicine Alumni Association on May 14, 1983.

Dr. Thomas L. Gross, Assistant to the Program Director at the same center, was honored with the Community Hospital Award for Research (1981) for his paper on the diagnosis of intrauterine growth retardation, and the Annual Prize Award for Research (1982) from the Central Association of Obstetricians and Gynecologists for his paper on transient tachypnea of the newborn.

Dr. Henry J. Binder, Program Director of the Yale General Clinical Research Center (Adult Section), has been awarded a Wellcome Visiting Professorship in Basic Medical Sciences for the 1983-84 year.

Dr. Seymour Reichlin, Professor of Medicine and Program Director of the General Clinical Research Center at New England Medical Center, was awarded the Berthold Medal of the German Endocrine Society for work on growth hormone and thyroid stimulating hormone regulation.

Dr. Gary Robertson, Professor of Medicine and Program Director of the GCRC at the University of Chicago, was chosen to give the annual "state-of-the-art" lecture at the 1982 Meeting of the Central Society for Clinical Research.

Dr. John D. Johnson, Associate Professor of Pediatrics and Associate Director of the GCRC at the University of New Mexico, has been elected President of the Society for Pediatric Research for 1983.

Dr. Alan F. Hofmann, Professor of Medicine and Co-Program Director of the GCRC at the University of California, San Diego, was awarded the Phillip Bushell Trust Visiting Lectureship of the Gastroenterological Society of Australia, 1983.

Dr. Myron Genel, Program Director of the Pediatric GCRC at Yale University School of Medicine, is the recipient of a Robert Wood Johnson Health Policy Fellowship from the Institute of Medicine of the National Academy of Sciences.

RESEARCH HIGHLIGHTS

The following biomedical highlights represent research that has been carried out in the centers.

Pathogenesis

LYME DISEASE

A newly recognized spirochete has been isolated from patients with Lyme disease, a type of chronic arthritis discovered in 1975. This bacterium, which is carried by ticks that transmit Lyme disease, seems to be the causative agent of this condition.

It has been learned that tetracycline is the most effective therapy for the early manifestations of this disease.

MENINGOCOCCAL DISEASE

Decreased function of complement, the collective name for a group of key components of the immune system, is common in patients with a first episode of non-epidemic meningococcal infection. A hereditary defect in the complement system or a complement-depleting underlying illness may thus be an important risk factor in the development of this serious disease.

INFECTIONS

Some infants who are highly susceptible to colds, flu, and other infections become as robust as their playmates by age four. This condition has been discovered to be due sometimes to a temporary immune deficiency called

transient hypogammaglobulinemia. Although the fundamental cause of this disorder is unknown, it results from a delay in the beginning of antibody production by infants, which normally occurs at about six months of age.

DRUG-INDUCED ANEMIA

Dapsone, a drug used to treat skin diseases, is secreted into breast milk, and can cause hemolytic anemia in lactating women and their breast-fed infants. This drug is an antibacterial agent commonly used to treat chronic skin disorders, particularly dermatitis herpetiformis and leprosy.

ACQUIRED IMMUNODEFICIENCY SYNDROME

Some apparently healthy patients with classic hemophilia have abnormalities in cell-mediated immunity which resemble closely those of acquired immunodeficiency syndrome (AIDS). Patients with these abnormalities seem to be susceptible to opportunistic infections. The abnormalities have been found in patients treated with lyophilized antihemophilia factor (pooled from many donors), and not in those treated with cryoprecipitate (obtained from a small number of donors).

AIDS has also been discovered in some living infants, most of whom were born to promiscuous or drug-addicted mothers. Characteristic clinical features of infants are small birth weight, failure to thrive, lung disease, recurrent infections, and enlarged lymph glands, liver, and spleen.

GROWTH HORMONE RELEASE

The secretion of growth hormone can be stimulated by a newly discovered hormone called growth hormone releasing factor (GRF). The hormone was isolated from a pancreatic tumor removed from a patient with acromegaly, a condition caused by excessive levels of growth hormone. GRF has potential application to many human health problems, including short stature, aging, and debilitating conditions such as burns, trauma, and major surgery. It also may have applications in agriculture as a safe and effective way of regulating the growth of domestic animals.

KIDNEY STONES

The current programs of intravenous nutrition used in intensive care nurseries have been shown to cause hypercalciuria (elevated blood calcium) in a majority of infants. This can result in renal stones.

NUTRITION

Certain physiologically indispensable compounds, non-essential in the diet of normal persons, become essential for sick individuals who have lost the capacity for synthesis at an adequate rate. Widespread use of synthetic intravenous solutions containing only essential nutrients has created the setting for new dietary deficiencies.

ARTERIOSCLEROSIS

The relationship between cigarette smoking and arteriosclerosis is well-known, but its mechanisms remain obscure. Recently it has been found that production by the kidneys of prostacyclin, which plays an important role in regulating blood clotting and the deposition of lipids in blood vessels, is reduced after smoking. This suggests that the harmful effect of smoking on arteries is a result of chronic inhibition of prostacyclin release.

DIABETES

Counter-regulatory hormones is the term applied to certain secretions which raise the blood sugar in normal and diabetic persons. A diabetic patient was recently described who demonstrated a complete failure to release these hormones, resulting in frequent and severe insulin reactions. The report of this patient has drawn wide attention in the scientific and popular media because it has focused attention on the dangers of intensified insulin therapy, especially in those patients who have a special susceptibility to hypoglycemia.

FAILURE OF MENSTRUATION

Long-distance running, which has become a popular American pastime, is associated with amenorrhea (failure of menstruation) in some women. Although the cause of this amenorrhea is not known, recent investigations into the problem have produced remarkable findings about the hormonal effects of exercise. For example, the levels of both luteinizing hormone (a secretion from the pituitary which stimulates the gonads) and testosterone increase in anticipation of exercise. Such increases occur even if exercise is not conducted, if the subject believes that it will be.

HYPERSENSITIVITY LUNG DISEASE

Two new environmental antigens capable of causing hypersensitivity pneumonia have been discovered. One of these is a fungus called Cephalosporium, which contaminates humidifiers and overflow sewage. Another is Streptomyces albus, a bacterium added to soil to enhance its nutritional value to plants.

CHRONIC INTESTINAL PSEUDO-OBSTRUCTION

Intestinal movements are normally controlled by intestinal muscles, intestinal nerves, and gastrointestinal hormones. Abnormal muscle is a much more common cause of impairment of intestinal movement than either nerve or muscle disease. A related major discovery is that some patients with pseudo-obstruction suffer from a new type of genetic disease in which patients have only intestinal (or smooth) muscle disease without involvement of the body muscle or heart muscle. The new disorder has been termed familial visceral myopathy.

ARTHRITIS

Epstein-Barr virus, a herpes-like agent which has been found in cell cultures of Burkitt's lymphoma and in cases of infectious mononucleosis, stimulates the secretion of autoantibodies (proteins that attack the body's own tissue) and antibody-producing cells in bone marrow. One of these autoantibodies is rheumatoid factor, a substance often produced in cases of rheumatoid arthritis. This clue has stimulated anew the search for viral agents in arthritis.

ASTHMA

Investigation of five persons who have experienced life-threatening asthma attacks following restaurant meals has revealed that all of them are sensitive to sulfite, which is commonly used as a preservative in drugs, beer, wine, seafood, potatoes, dried fruit and vegetables, avocados, and salads. Further studies on other asthmatics suggest that up to 10 percent of them, or as many as 1 million persons in the U.S., may be sensitive to sulfite preservatives.

Prevention

BIRTH DEFECTS

The risk of harm to the fetus from smoking by the pregnant woman is well-known. Now there is evidence to support the idea that the fetus may be harmed if a woman's spouse smokes, even if she does not. When a non-smoking pregnant woman is exposed to the cigarette smoke of other people, the blood of her fetus contains significant amounts of tobacco smoke metabolites.

BLINDNESS

Patients with signs of partial visual loss caused by pseudotumor cerebri, an increase in intracranial pressure of unknown origin, may be at high risk of permanent severe visual loss, especially if they have hypertension or are given steroids as treatment. Repeated tests of visual acuity and photographs of the optic nerve may be necessary to indicate when surgery should be undertaken to reduce intracranial pressure.

Diagnosis and Prognosis

SCREENING FOR THYROID CANCER

Studies have been carried out for years on familial medullary thyroid carcinoma, a hereditary form of cancer. The investigators have now learned that screening should begin by age 5 and can be stopped after age 35, effecting a considerable economy in the cost of medical care of these people. Virtually no one from a susceptible kindred will develop the disease if no signs of it are present at age 35. Even by age 25, only 1 in 10 unaffected susceptible persons will later prove to have the disease.

SHORT STATURE

A new office technique can be used to screen short children for growth hormone deficiency by means of anthropomorphic measurements. The method takes advantage of the tendency of short, growth hormone-deficient children to exhibit an increased adipose mass because of loss of fat-mobilizing actions of growth hormone.

LABOR AND DELIVERY

An ultrasonic transit-time monitoring system safely records dilation of the cervix during delivery. The device reduces the need for manual pelvic examinations, decreasing patient discomfort and the risk of infection while increasing the accuracy of the information obtained.

SUICIDE

Primary endogenous depression is frequently accompanied by a failure of the drug dexamethasone to cause suppression of cortisol secretion (dexamethasone suppression test). An important new finding is that persistence of a positive test (non-suppression) after clinical recovery from the depression predicts a poor eventual outcome, including a high suicide rate.

The dexamethasone suppression test also has been modified to improve its accuracy, allowing a distinction between alcoholics with primary depression and those whose depression is caused by alcohol. The distinction is important, because treatments for the two types of patients are very different.

FETAL BEHAVIOR

By the use of sophisticated electronic instruments and computerized analysis, it has been learned that the fluctuation of fetal movements are not random but are cyclic and rhythmic. The cyclic pattern resembles that previously seen in newborns, suggesting a common process controlling pre- and post-natal activity. This study technique will provide a new non-invasive means of examining neurobehavioral organization near the end of pregnancy, possibly with clinical significance.

Therapy

HYPERTENSION

When patients with hypertension who are accustomed to eating relatively high concentrations of salt are maintained on a low-salt diet for several months, they eventually shift their salt preference to lower concentrations. The potential importance of this finding is that it indicates patients who at first have difficulty adhering to a low-salt diet may after some time find it easier and more pleasant to eat foods with a lower salt content.

LIVER DISEASE

A review of the experience with distal splenorenal shunts, an operation for esophageal varices, shows 93 percent control of bleeding, an operative mortality of 40 percent, and a 5-year survival of 65 percent. These results are much superior to those previously achieved with other kinds of shunts.

ANGINA

The addition of nifedipine (a calcium channel-blocking drug) to conventional treatment decreased the incidence of sudden death or heart attacks in patients with unstable angina (heart pain not closely related to exercise), a condition with a poor long-term prognosis. This improvement was especially marked in those patients who had certain EKG changes, known as ST segment elevation, during pain. In these patients, it is likely that the drug acts by preventing coronary artery spasm.

FAILURE OF PUBERTY

Puberty is normally heralded by the appearance of episodic secretion of gonadotropins, pituitary hormones which activate the gonads. Men with idiopathic hypogonadotropic hypogonadism have an abnormality in gonadotropin release and do not undergo normal puberty. Now, long-term pulsatile subcutaneous administration of gonadotropin-releasing hormone, administered by a portable infusion pump, has been used successfully to produce signs of puberty in these subjects.

HEART DISEASE

Glipizide, an investigational drug that reduces the blood sugar, also produces changes in lipoprotein metabolism that may lessen the risk of atherosclerotic heart disease. Used to treat non-insulin-dependent diabetes mellitus, glipizide produces favorable changes in the concentrations of triglycerides, cholesterol, low-density lipoprotein-cholesterol, and high-density lipoprotein-cholesterol.

LIVER TRANSPLANTATION

An NIH Consensus Development Panel has concluded that liver transplantation, a procedure developed in this country primarily through GCRC-based research, is a useful therapy that deserves broader application for end-stage liver disease. The use of the new immunosuppressive drug cyclosporin A has significantly increased the success rate of this operation by reducing the body's tendency to reject transplanted tissue.

MULTIPLE SCLEROSIS

Progressive multiple sclerosis (MS) may be stabilized by short-term intensive immunosuppressive therapy with cyclophosphamides and ACTH. This is not a cure for the disease, and its long-term efficacy remains to be assessed, but

it suggests that it may be possible to devise general or specific immunosuppressive regimens which will control MS.

KIDNEY STONES

The FDA has approved a new drug, sodium cellulose phosphate, which in 15 years of GCRC clinical trials has shown effectiveness in preventing painful stone formation in patients with severe forms of absorptive hypercalciuria. This common stone-forming disorder is associated with increased absorption of calcium from the diet. The new drug prevents this by binding calcium from the food in the patient's digestive system. Kidney stone disease is an important public health problem, affecting about 0.5 percent of U.S. citizens, resulting in considerable suffering and many lost work days, and costing hundreds of millions of dollars in medical expenses annually.

SEVERE COMBINED IMMUNODEFICIENCY SYNDROME

Bone marrow from a non-compatible donor has been transplanted successfully into a four-month-old patient with severe combined immunodeficiency disease. The patient has good immune function and there is no sign of graft-versus-host disease (GVHD). A major hazard in this type of transplantation, GVHD was prevented by treating the donor bone marrow before transplantation, and the patient herself after transplantation. Treatment consisted of monoclonal antibodies produced by a tissue culture all descended from a single cell, against the donor's mature T lymphocytes, the cells which ordinarily recognize the host as foreign and cause GVHD.

FETAL ABNORMALITIES: HYDROCEPHALUS

An operation which can be performed on an infant in the uterus has been developed to improve the management of hydrocephalus (excess fluid within the brain). It involves placing a shunt between the lateral ventricle (fluid space within the brain) when the fetus is at 20 weeks gestation, or as soon as progressive hydrocephalus is detected. A similar operative procedure has been devised to relieve kidney obstruction in the fetus. These developments have encouraged a major new effort to diagnose such congenital malformations before birth.

GAUCHER'S DISEASE

Gaucher's disease, a hereditary disorder, appears to result from an enzyme deficiency which causes storage of unmetabolized complex lipids in cells called macrophages, which are located in bone, lung, liver, and spleen. Because macrophages are derived from hematopoietic (blood-forming) stem cells, bone marrow transplantation was attempted in a patient with this disease. Successful transplantation led to correction of the enzyme deficiency, marked reduction in the number of abnormal cells, and a marked decrease in the size of the patient's enlarged liver. This success points the way to a potential cure for victims of this destructive disorder.

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS): KAPOSI'S SARCOMA

AIDS is an important new disease, presumably caused by an infectious agent which results in the acquisition of a defect in the cellular immune system. The defect causes an increased susceptibility to infection by a variety of otherwise opportunistic organisms, and to a cancer called Kaposi's sarcoma. The therapy of patients with Kaposi's sarcoma has been unsatisfactory. Although many patients respond to chemotherapy, the use of chemotherapeutic drugs appears to increase the risk of opportunistic infection, probably by further induction of immune deficiency. A new approach is to use immune modulators in the therapy of this disease. In a controlled, prospective randomized study, alpha-2 recombinant (bacterially made) DNA interferon was used. Although the number of patients treated on this protocol was small and follow-up of patients' responses has been going on for less than six months, high-dose interferon therapy appears to have a beneficial effect on this otherwise difficult disease.

HEART AND LUNG TRANSPLANTATION

Cyclosporin, a naturally occurring immunosuppressive agent, has become the cornerstone of maintenance therapy in patients receiving many types of organ transplantation. During the past year, among 22 patients undergoing cardiac transplantation or retransplantation who were treated with cyclosporin at one center, the hospital discharge rate was 90 percent. Actuarial analysis of one-year survival is 90 percent, and rehabilitation has been achieved in 90 percent of the long-term survivors.

OBESITY

d-Fenfluramine, a drug which mimics the action of the natural hormone serotonin, selectively inhibits carbohydrate intake. On this drug, but not on placebos, obese subjects who claimed to have excessive appetites for carbohydrates maintained their protein intakes but decreased their carbohydrate intakes when allowed to choose freely at meals and from snack vending machines.

LEUKEMIAS

Certain hematologic malignancies not responsive to the usual therapies will often respond to high-dose cyclosphosphamide and total body irradiation followed by transplantation of the patient's own marrow, obtained during a remission from leukemia and stored frozen. The bone marrow can be stored at liquid nitrogen temperature for at least two years.

SHORT STATURE

Recent studies indicate that growth hormone (GH) prepared biosynthetically, using recombinant DNA techniques, is safe and effective in inducing growth in GH-deficient children. This is important because GH previously has been obtainable only from human pituitary glands.

WARTS AND OTHER VIRAL INFECTIONS

Human interferon, an anti-viral substance obtained from white blood cells, has been found to be effective against extensive, long-standing warts. Studies recently undertaken are thought to provide an indication that interferon may be useful not only against acute viral infections but also against virus-induced tumors.

DIABETES

Insulin treatment of diabetes requires repeated injections. Better control of the disease and probably fewer long-term complications result from frequent injections or treatment by infusion pumps, but many patients are reluctant to use such therapies. Recent studies indicate that insulin mixed with a bile salt and administered intra-nasally as an aerosol spray has an effect like that of insulin administered into a vein, and can be used to control the blood sugar, especially after meals.

A new system for delivering insulin directly into the peritoneal cavity avoids recurrent and sometimes life-threatening infections caused by administering the drug intravenously, an unusual route of injection reserved for diabetics whose tissue beneath the skin inactivates insulin administered in the usual way. The new system can be used successfully by patients with the recently developed, semi-automatic implantable insulin pumps.

Diabetologists and nutritionists have long believed that simple carbohydrates such as sugars cause rapid rises in blood sugar and blood insulin, while complex carbohydrates like starches take longer to be absorbed, resulting in slower and more moderate rises. Direct tests of these assumptions at a GCRC have shown, however, that the effects of a particular carbohydrate-containing food on blood sugar are not predictable by such a simple general rule, and must be tested directly. According to an editorial in Science, these findings are of major importance to the way diabetics structure their diets, especially with respect to the time-honored "exchange lists," which give them choices of equal amounts of carbohydrate from a variety of foods.

Although diabetics may not need to fear a moderate amount of sucrose in a mixed meal, recent evidence supports old ideas that fructose, which can be incorporated into food products as a sweetener, may be preferable to sucrose for blood sugar control. This is an especially important finding now that new methods have been developed for preparing large amounts of fructose inexpensively.

Regular exercise increases the efficiency of glucose metabolism, a finding of importance to the management of diabetes. Jogging, bicycling, or exercise programs lead to enhanced insulin action and reduced plasma glucose levels.

Monitoring of diabetic patients who are pregnant has revealed that there is heightened insulin sensitivity during the first trimester, especially between

weeks 9 and 13, and that sporadic hypoglycemia (low blood sugar) is common. The insulin dosage should be adjusted at this stage of pregnancy to mitigate hypoglycemic reactions.

"Closed-loop" devices for intravenous insulin administration (insulin infusion controlled by continuous monitoring of the blood sugar) can maintain the blood sugar of diabetic persons at normal level. They are important as a way of determining optimal schedules for subcutaneous insulin delivery with portable infusion pumps (open-loop devices) or by frequent conventional insulin injections, but their use is limited because of their expense, inconvenience, the need for specially trained medical personnel, and the need for uninterrupted venous blood flow. A newly developed, simplified, closed-loop system, which uses nursing personnel trained in measuring blood glucose at the bedside and an intravenous fluid delivery system routinely used in most hospitals, gives results which correlate well with those obtained by the more complex method. The simplified procedure should prove useful and economical for diabetic patients who require tight blood sugar control, such as those who are pregnant, undergoing surgery, or in need of metabolic regulation.

IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)

ITP is a disease of unknown cause in which a very low level of blood platelets leads to excessive bleeding. Treatment usually involves removal of the spleen or immunosuppressive therapy, but the former greatly increases the risk of overwhelming fatal infections and the latter has many undesirable side effects. New results indicate that intravenous gamma globulin effectively elevates the platelet count in chronic ITP, diminishing the risk of bleeding and possibly eliminating the need for more toxic therapies.

PROSTATE CANCER

Analogs of gonadotropin-releasing hormone, produced by the brain, have been studied for their mechanism of action as anti-prostate cancer agents. A high response rate and a lack of serious side effects make it likely that these compounds will replace estrogens as the preferred forms of hormonal treatment for metastatic complications of this common malignancy.

PRECOCIOUS PUBERTY

Modification of the brain hormone LRF (luteinizing hormone releasing factor) produces a compound which is effective against one of the major forms of precocious puberty, that which is of pituitary gland origin rather than gonadal origin. The modified material works by producing a reduction in the number of receptors for the normal hormone in the pituitary gland.

WORKSHOPS, CONFERENCES, AND MEETINGS

PROGRAM DIRECTORS' MEETING

In December 1982, the Association of Clinical Research Center Program Directors conducted a three-day conference in Scottsdale, Arizona, on the future of the program. The meeting consisted of a series of workshops which addressed the role of the CRCs in the promotion of clinical investigation, the diversification of CRC utilization, the promotion of collaborative, cooperative, and industry-related research among centers, the development of new technologies for the centers, and the examination of the organization and operation of the centers.

An important concern of the discussions was the diminishing opportunities for patient-based investigations. The number of GCRCs has decreased by 20 percent from its maximum, the disapproval rate is nearly twice as great for NIH research grant proposals that involve human subjects as for those that do not, and the priority scores assigned to human subject research proposals are, on the average, much lower. Meanwhile, the major focus of clinical investigation has shifted over the last 20 years from bedside observations to sophisticated, biochemical analyses that require laboratories. Although this has been an exciting scientific change, it has contributed to perceptions that laboratory investigation into fundamental mechanisms produces quicker results and higher esteem, and is more likely to be funded. Young investigators, and even some established ones, have been turning away from clinical research in favor of laboratory studies, a problem well-recognized in the scientific press.

The program directors made a number of recommendations for actions to meet the need for more clinical research, which has become more important than ever now that rapid advances in basic science have produced opportunities for the development of better understanding and management of disease. To ensure that clinical projects receive fair review, the group proposed that a greater effort be made to identify qualified, experienced clinical investigators to serve on review groups concerned with human subject proposals. To meet the criticism that human subject grant proposals are less competitive because of weaknesses in study design, they propose that more attention be given to support for training for a career in clinical research, especially in basic biology, biostatistics, and epidemiology. There is a need for more innovative approaches to research training for physicians; the CRCs could provide resources and opportunities that would complement categorical institute training programs.

The GCRC Program has already recognized that maturation as a clinical investigator requires some guidance beyond formal training years, and has initiated the postfellowship Clinical Associate Physician (CAP) Program. To encourage established productive clinical investigators to remain in patient-related work instead of turning toward laboratory studies only, the program directors suggest a mid-career award analogous to the CAP. This would not only help support such investigators during their most productive

years, it also would help increase the number of clinical scientist role models for medical students and house officers.

Finally, the program directors believe that the program should have a role in stimulating the application of rapidly advancing modern-day technology to the GCRCs. The GCRC-based CLINFO system, which can revolutionize the way investigators manage their data, could become the basis of a network for data exchange and collaborative efforts. In a similar way, modern separation and analysis methods (high-performance liquid chromatography, gas chromatography-mass spectrometry, nuclear magnetic resonance, etc.) could make the core laboratories centers of high-quality research throughout those institutions with funded GCRCs.

CLINICAL DATA MANAGEMENT AND ANALYSIS ADVISORY COMMITTEE

A Clinical Data Management and Analysis Advisory Committee meeting was held on May 12-13, 1983, at the NIH to discuss the attributes and capabilities of current data management information systems for clinical research (CLINFO and other systems) and to explore the potential for a new system designed to operate on microcomputers. The requirements of the system were to be specified and its parameters defined. Consideration was given to taking advantage of the extensive software, hardware, data management systems, and graphics capabilities being developed for microcomputers.

The members of the committee were experts in clinical research, computer technology and information sciences, and clinical epidemiology and statistics.

The committee was asked to identify and rank the needs for development of special software with wide applications to clinical investigators. Because the market is small, it is believed that there is a need for government-sponsored programs to develop software of general utility such as nutritional or compartmental analysis programs. The committee considered the advantages of general systems to facilitate support of clinical trials, and the potential of such systems to support clinical data bases.

The committee made preliminary recommendations and suggested areas for further exploration, as follows:

- To establish a mail net within the GCRC CLINFOs, starting with four or five centers in a pilot study, under a grant mechanism
- To determine the feasibility of incorporating an outpatient management module in CLINFO
- To continue encouraging the development of CLINFO Plus by Bolt, Beranek and Newman

- o To determine the feasibility of developing alternative plans for CLINFO in portable software

- o To explore the possibility of adapting existing commercial software to CLINFO requirements

- o To explore the feasibility of expanding statistics and experimental methods, e.g., automatic learning and numerical simulation

- o To establish a subcommittee to determine the feasiblity of developing American National Standards Institute (ANSI) standards for CLINFO

- o To examine and redefine the role of the system manager

- o To characterize needs of clinical investigators and clinical investigation in the 1980s

- o To establish and develop special interest groups in areas such as nutritional analysis, clinical trials, system managers, and compartmental analysis.

CLINFO SYSTEM MANAGERS MEETING

The Organization of System Managers met in Bethesda, Maryland, to assess the status of the CLINFO system and to discuss possible future developments. An important contribution came from CLINFO users, whose needs and suggestions had been surveyed and analyzed. The system managers discussed common problems in four work groups: Data Analysis; Data Base Management; Transfer of Data; and Radioimmunoassays. One area of interest to all system managers was the implementation of tutorials to help users with common statistical problems.

As a result of these meetings, Bolt, Beranek and Newman, the CLINFO purveyor, has incorporated 13 important changes into the CLINFO software package and will use other suggestions made at the meeting as a guide to future efforts to update the system.

CLINFO COMMUNICATIONS

A CLINFO communications subgroup met on July 7, 1983, to discuss the feasibility of facilitating communications among GCRCs. The CLINFO system could be used to address issues and answer questions in a simple and speedy way. Technical aspects of the system will be discussed by system managers and investigator communications with respect to collaborative studies. It is expected that communications between the Duke CLINFO and the Cincinnati CLINFO, using Duke Cardiology as the host and coordinator, will be completed by late December. Data from this initial feasibility study will be presented to the next ad hoc CLINFO committee meeting. Dr. C. Franklin Starmer of Duke University is installing and testing communication software packages (public

domain) that will allow DEC 11s and VAXs to do mail bulletin boards and exchange files.

NATIONAL ASSOCIATION OF ADMINISTRATIVE COORDINATORS

The National Association of Administrative Coordinators of the General Clinical Research Centers held a two-day conference in May 1983 in Washington, D.C. Workshops on administrative policies, procedures, and general guidelines were conducted. Nearly one-third of the coordinators attended the association conference for the first time. The workshops were informative and helpful to the attendees from the centers and the branch staff.

NATIONAL ASSOCIATION OF RESEARCH NURSES AND DIETITIANS

The annual meeting of the National Association of Research Nurses and Dietitians, titled the "Rocky Mountain Clinical Research Symposium," was held September 7-10, 1983, at Keystone, Colorado. It was presented by the adult, pediatric, and neonatal centers at the University of Colorado. The keynote address was given by the Director of the GCRC Branch. The goals of this meeting were:

- To promote continuing education to improve the science and art of clinical research for the expansion of comprehensive health care
- To unite as a professional team, improving national knowledge, ideas, problems, teaching methods, and learning techniques in the research field
- To define, evaluate, and expand the roles of research nurses and dietitians
- To foster the highest professional and ethical standards by stimulating a team concept in the specialty area of clinical research.

SUBCOMMITTEE ON SMALL CLINICAL RESEARCH CENTERS

Noting that a diverse spectrum of centers exist whose research resources are provided by the GCRC Program, this subcommittee offered a further definition of smaller centers which could provide clinical research for a corps of excellent investigators who would otherwise be unable to perform their clinical studies. The smaller centers would not be mirror images of the large CRCs, but would, nevertheless, be CRCs and would not be considered different entities. The centers would not, therefore, have a separate name, but would have a separate description. It was recommended that this description be included in the CRC guidelines under the title of "Minimum Requirements for a Center." Members indicated that those centers meeting such minimum requirements might either be sizable centers with several B-type patients, most of whose basic costs are provided by both the institution and third-party insurance carriers; or they might be centers with a few excellent

investigators with diversified interests in areas such as metabolism or gastroenterology where support for their studies is difficult to obtain. The overall consideration was that the smaller centers have no fixed model.

Further, the subcommittee recommended that the following requirements be considered as minimum standards for a CRC:

- o A discrete defined geographical area
- o A program director, supported at 50 percent FTE, and an administrative secretary, supported at an FTE appropriate for the activity level
- o Space provided within the confines of the defined unit for the program director and the administrative secretary
- o Three or more established investigators with multi-disciplinary studies
- o Two research nurses.

Provisions for other support are to be made available on the basis of the level of research activity. To facilitate increased institutional support, additional nursing and dietary services will be available on a per diem basis.

SUBCOMMITTEE ON DATA MANAGEMENT

The Subcommittee on Data Management held meetings before all the GCRC Advisory Committee meetings to discuss immediate and future needs of the CLINFO system.

The concern with immediate needs was mainly with the review of the applications for new CLINFO systems. Twenty-one applications are expected to be reviewed during the next two review cycles. The subcommittee members agreed that the GCRC Advisory Committee will review the scientific aspects of the applications, but that technical aspects will have to be reviewed by ad hoc committee members who are experts in the field. The committee believes that a successful review depends on the liaison between the GCRC Committee and ad hoc advisors. The subcommittee also suggested that the review of the system manager should be reconsidered. Future needs for CLINFO were discussed after recommendations made by the CLINFO II ad hoc advisory committee were reviewed. The subcommittee concurred with the recommendations made by this committee.

SUBCOMMITTEE ON TECHNOLOGY

The Subcommittee on Technology discussed mass spectrometry (MS) needs of GCRC investigators and how to fulfill them. At an earlier meeting, the possibility of enlarging biotechnology MS sites to accommodate clinical investigators had been discussed. At this meeting, a proposal from staff of

the Biotechnology Resources and GCRC Programs was discussed which proposes that GCRC investigators in need of MS resources contact MS sites and offer to pay for costs of travel, consumable supplies, and machine time. These costs would be taken up by the GCRC Program. Such projects would have to undergo scientific review.

A second discussion concerned a proposal from the CLINSPEC facility in South Carolina to extend its program from support for investigators during an initial research phase to collaboration on an ongoing basis (two to three years). It would include visits of the investigators to the CLINSPEC site, instructions in the use of a brand new MS facility which is much less costly than the conventional type in case they are awarded to GCRCs in the future, and instruction of investigators who do not have MS facilities in use of facilities that are close to their home sites. A Ph.D. from the CLINSPEC site would also visit novice investigators at their sites. The subcommittee members agreed that the proposal should be considered by the GCRC Program.

PUBLICATIONS

The GCRC Program has been in operation for more than 20 years, but the program lacked a comprehensive review of its scientific contributions. Thus, the program decided to evaluate all major scientific contributions that have been made since the program was initiated. The project has been divided into two phases.

The first phase of this evaluation was directed at obtaining lists of significant publications from the GCRCs. With advice and guidance from the GCRC committee and the extant GCRCs, areas of clinical medicine were identified in which major advances have taken place in the past 20 years. A list of 31 categories and more than 200 sub-categories was developed from this effort. Center program directors were given this list and asked to identify those articles which they thought were most significant, according to a suggested list of criteria. This exercise resulted in the submission to the GCRC Branch of more than 7,000 articles from 77 GCRCs.

The second phase is to continue evaluating articles and developing reports on selected topics. For this purpose, workshops have been held and expert consultants have been asked for evaluations. The first four topics selected were neuroscience, diabetes, neonatology and related immunology, and hypertension. A GCRC committee member chaired a workshop of consultants on each topic. The consultants presented special sub-topic reports to the chairperson, who compiled and edited the sub-topic sections. The reports on diabetes and neurosciences have been completed and distributed. The remaining two reports are ready for publication. Additional workshops are planned, including one on nutrition, and work on them has begun.

SPECIAL EVENTS

Three GCRCs held 20th Anniversary celebrations, all attended by the Director, DRR. These included the GCRC at the University of Alabama at Birmingham,

the GCRC at the University of Michigan (Dr. Donald Fredrickson, former Director, NIH, was the key speaker), and the GCRC at the Children's Hospital, Boston. A new GCRC was dedicated at the VA Hospital in San Antonio, Texas, the first center to be located in a VA Hospital.

FUTURE DIRECTIONS

CLINICAL RESEARCH RESOURCES

During the coming year, the program plans to fund 75 centers. Applications for smaller centers will be accepted and funded according to merit. An emphasis on outpatient studies will be continued. A general examination of questions about the number and kinds of off-center beds and activities and the number and kinds of tests to be performed in core laboratories will be undertaken by the program directors during the next two years. Recommendations from program directors will be submitted to program advisory groups for consideration and action. The resource instrumentation needs for larger, shared instruments will be surveyed and defined, and plans for meeting high-priority needs will be developed.

CLINICAL RESEARCH FOR DATA MANAGEMENT AND ANALYSIS SYSTEMS

The GCRC Program has deployed the CLINFO Data Management System in 22 centers and currently has 20 additional applications to review. More centers are planning to apply. The Advisory Committee and Council have noted that a data management system such as CLINFO is becoming a standard for a GCRC. If additional CLINFO systems can be funded within the next two years, the rudiments of a program-wide data management system will be in place. This system will permit both private and shared data bases. The communication software, which will permit file transfer and electronic mail functions, is being tested and will be deployed shortly. This will permit preliminary testing of the potential utility of a clinical research data management communication network.

Concurrent with the deployment of CLINFO, planning for further development of the system is well under way. With the encouragement of the ad hoc CLINFO advisory committee, Bolt, Beranek and Newman, Inc. is planning an enhanced version of CLINFO, called CLINFO Plus. Alternative systems will be evaluated and funded as appropriate. Additional projects contemplated by this committee will be enumerated and given priority next year.

The role of the system managers will be examined and updated. Because of expanded capacity for data manipulation, statistical planning will become more necessary for clinical research projects. Applications for supplementary statistical support will be considered on the basis of merit.

TRAINING

The Clinical Research Associate Program and the Medical Student Program have highlighted Clinical Research Center contributions to clinical research

training. Recently, several centers have expressed strong interest in training activities using the centers as the investigative resource. During the coming year, the role of Clinical Research Centers in training will be examined in detail.

OPERATIONS

Consideration will also be given to appropriate modification of the GCRC Program guidelines to ensure the integrity of the scientific data obtained in center studies. Additional operational questions will be addressed during the coming year, including the potential impact of the Division of Research Grant payment schedule on the availability of clinical research dollars.

Table I

ESTIMATED TYPICAL CENTER
(75 Centers)

FUNDED FY 83

8 beds

PERSONNEL	FTE	Amount (thousands)	
Professional	1.1	$ 77	
Administrative	1.4	30	
Laboratory	2.4	53	
Dietary	3.3	57	
Nursing	11.8	265	
Other 1/	.9	25	
Fringe Benefits (21.3%)		108	
	20.9	$ 615	$ 615
HOSPITALIZATION			
Routine/Per Diem/Scatter Bed		$ 299	
696 B Patient Days X $144		(100)	
375 C Patient Days X $144		(54)	
1409 A Patient Days X $87 (Ancillaries)		123	
1437 Outpatient visits X $22 (Ancillaries)		32	
		$ 300	300
TRAVEL			3
SUPPLIES, EQUIPMENT, OTHER, ALTERATIONS & RENOVATIONS			62
TOTAL DIRECT COST			$ 980
INDIRECT COSTS (8% of the Total Direct Costs)			74
TOTAL DIRECT AND INDIRECT COST			$ 1,054
LESS UNOBLIGATED BALANCE			(52)
			$ 1,002

1/ Includes 33.53 FTE Clinical Associate Physician positions

Research Patients -- Category A - Those patients admitted to the GCRC to participate in a research protocol.

Research Service Patients -- Category B - Those patients admitted to the GCRC primarily for the purpose of diagnosis or treatment according to established procedures who are also participating in a GCRC research protocol.

Non-Research Patients -- Category C - Those patients admitted to the GCRC solely for the purpose of diagnosis or treatment according to established procedures, but who are not participating in a research protocol.

Table II

GCRC PROGRAM, 1969 - 1983

FY	CENTERS	FUNDED POSITIONS FTE	FUNDED BEDS	PATIENT DAYS A & B & C	OUTPATIENT VISITS	APPORTIONMENT (in thousands)
83	74	1,547	595	185,974 1/	106,327	$ 74,520
82	75	1,534	595	187,299	119,361	64,384
81	75	1,555	592	181,519	108,053	60,148
80	75	1,694	602	195,145	101,966	56,720
79	74	1,640	613	198,500	86,215	51,941
78	79	1,708	633 2/	206,767	71,049	51,946
77	82	1,679	755	204,369	65,130	47,283
76	84	1,725	784	222,488 3/	56,217	42,533
75	84	1,719	823	223,269	50,020	42,619
74	87	1,808	877	232,534	50,614	42,320
73	83	1,790	893	227,501	36,280	41,300
72	84	1,867	907	238,152	23,654	42,181
71	82	1,885	881	234,870	14,515	38,004
70	93	2,076	904	244,824	1,175 4/	35,004
69	93	2,298	1,023	245,943	--	35,004

1/ Awarded
2/ Excludes 73 beds used for C patients included prior to 1977
3/ 12-month period
4/ Initial year of outpatient program

Figure I

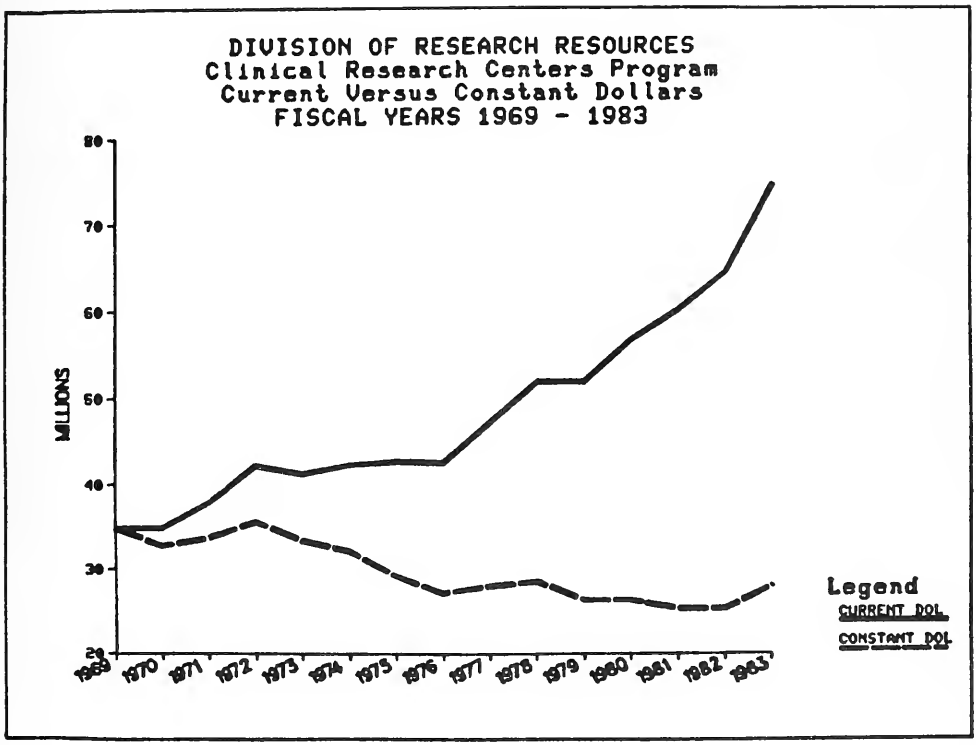

DIVISION OF RESEARCH RESOURCES
Clinical Research Centers Program
Current Versus Constant Dollars
FISCAL YEARS 1969 - 1983
MILLIONS
80
70
60
50
40
30
20
1969
1970
1971
1972
1973
1974
1975
1976
1977
1978
1979
1980
1981
1982
1983
Legend
CURRENT DOL
CONSTANT DOL

Table III

CLINFO & PROTOTYPES

Grant Number	Institution	FY Funded
RR-847	University of Virginia	83
RR-32	University of Alabama	83
RR-42	University of Michigan	83
RR-1066	Massachusetts General Hospital	82
RR-54	New England Medical Center	82
RR-211	University of Tennessee	82
RR-827	University of California, San Diego	82
RR-43	University of Southern California	81
RR-59	University of Iowa	81
RR-645	Columbia University	81
RR-833	Scripps Clinic	81
RR-888	Peter Bent Brigham Hospital	80
RR-585	Mayo Foundation	80
RR-400	University of Minnesota	80
RR-125	Yale University	80
RR-68	University of Cincinnati	80
RR-71	Mt. Sinai	80
RR-30	Duke University	79
RR-35	Johns Hopkins University	79
RR-37	University of Washington	78
RR-95	Vanderbilt University	78
RR-350	Baylor University	78

Table IV

CLINFO & PROTOTYPES

FY	No. of GCRC Sites	Amount Awarded	No. of Commercial Sites
83	22	$2,125,558	8
82	19	1,457,208	8
81	15	1,115,000	3
80	11	1,350,525	-
79	5	615,453	-
78	3	160,617	-

Minority Biomedical Research Support Program
Division of Research Resources

INTRODUCTION

MISSION

The Minority Biomedical Research Support (MBRS) Program seeks to relieve the problem of a shortage of minorities in biomedical research by strengthening institutional research capabilities and by promoting minority faculty and student research participation at eligible institutions. The MBRS initiatives are expected to produce minority scientists who will contribute significantly to the health sciences.

OBJECTIVES

The objective of the MBRS Program is to increase the number and quality of minority biomedical research scientists. The program accomplishes its objectives by:

- Strengthening the capability of eligible institutions to support the conduct of quality research in the health sciences
- Supporting faculty at eligible institutions as they initiate or expand their biomedical research interests and capabilities
- Supporting minority students engaged in research projects at the undergraduate and graduate levels to motivate and prepare them for careers in biomedical research.

PROGRAM DESCRIPTION

BACKGROUND

The MBRS Program was established to respond to the severe under-representation of minorities in biomedical research.

In Fiscal Year 1972, under the authority of Section 301(c) (now 301(a)(3)) of the Public Health Service Act, as amended (42 U.S.C. 241(d)), the Division of Research Resources (DRR) initiated the Minority Schools Biomedical Support Program, later shortened to the Minority Biomedical Support Program. In 1982, it was renamed the Minority Biomedical Research Support (MBRS) Program to emphasize its function as a research program. The program focuses on colleges, universities, and health professional schools in which 50 percent or more of the students are classified as minority. Other institutions, including those on Indian reservations, with substantial minority enrollments (but less than 50 percent) that demonstrate special commitment and assistance to minority faculty and students also are eligible. The program was expanded in 1975 to include two-year institutions.

The MBRS Program provides funds that allow faculty with full-time teaching appointments the opportunity through release time to engage in biomedical research. Equipment, supplies, and necessary renovations for approved research projects are supported by the program. Funds also are provided for student participation in research. Faculty at institutions that grant Ph.D. degrees are encouraged to participate as associate investigators; MBRS funds allow minority students to become involved in biomedical research projects that are funded from other sources. Consortia, collaborative arrangements, and travel to scientific meetings also are supported by the program.

GROWTH AND SCOPE OF THE PROGRAM

The program made the first grant awards, totaling $2 million, to 38 institutions in 1972. By 1983, the number of grantees had increased to 79 and the appropriation for the program had increased to $20.1 million.

The current grantee portfolio includes 5 two-year colleges and 32, 26, and 16 institutions which offer as their highest degree baccalaureate, masters, and doctorate degrees, respectively. The MBRS Program offers 4 grants that serve primarily American Indians, 45 that serve primarily blacks, 5 that serve primarily Puerto Ricans, and 2 that serve Hawaiians. The remainder serve a mixed population of minorities in large metropolitan areas and the Southwest. Five new MBRS programs were started in 1983.

A new initiative was implemented this year to upgrade instrumentation at MBRS institutions. Awards totalling $1.3 million were made to 20 of 40 applicants.

CO-FUNDING AND COST-SHARING WITH OTHER PROGRAMS

The MBRS Program established an administrative mechanism in Fiscal Year 1975 to involve other NIH institutes in funding some of the research projects at MBRS-supported institutions. The majority of the NIH institutes and the National Institute of Mental Health (NIMH) in ADAMHA participate in these funding agreements with the MBRS Program. The arrangements permit cooperating institutes to pay the costs for projects which are of direct concern to their stated missions and to assist the principal investigators in gaining individual research grant support from the categorical institutes. The MBRS Program provides for the overall review and management of these projects, including budget negotiations and monitoring of progress and accomplishments. The following table illustrates the co-funding activity in Fiscal Year 1983.

Co-funding and Interagency Agreements Activity
FY 1983

Institute	Funds	No. of Projects
NCI	$2,076,329	38
NHLBI	2,057,579	41
NIAID	93,348	2
NIADDK	1,185,867	37
NIDR	39,276	1
NIA	112,627	2
NEI	131,127	5
NICHD	351,778	9
NINCDS	62,403	2
NIEHS	221,379	3
NIMH	1,350,000	26
GCRC (DRR)	100,000	-
TOTALS	$7,781,713	166

RESEARCH HIGHLIGHTS

In general, the quality and productivity of faculty and students participating in the MBRS Program have continued to improve. In Fiscal Year 1983, the program supported positions for 894 undergraduate students, 340 graduate students, and 639 faculty. Research accomplishments were described in 770 scientific papers published by MBRS faculty and students and in 824 faculty and 672 student presentations at scientific meetings. For purposes of comparison, Figure I shows trends from 1974 to 1982.

INSTITUTIONAL DEVELOPMENT

Approximately 547 research projects were conducted at grantee institutions in Fiscal Year 1983, including 166 projects co-funded by 10 NIH institutes and NIMH. Areas of research ranged from clinical studies on hypertension to recombinant DNA technology. The diverse nature and sophistication of this research are in marked contrast to studies conducted during the early years of the MBRS Program. To bring about improvements, the program supported contemporary research equipment and other resources at grantee institutions; this attracted more research-oriented faculty, enhanced instructional capabilities in science laboratories, and aided recruitment of students.

Agreements with other DRR programs also have bolstered institutional research capability. The General Clinical Research Centers Program awarded a grant to Meharry Medical College to assist in the development of a small clinical research center, and the Biotechnology Resources Program has provided funding and technical support for the establishment of a PROPHET computer system at five MBRS institutions. This system manipulates, analyzes, and transmits

research data. Two workshops conducted in Puerto Rico by DRR staff stimulated the University of Puerto Rico to apply for a PROPHET system grant. The grant has been awarded, making the University of Puerto Rico the sixth PROPHET site at an MBRS institution.

Institutional research capability also was enhanced in 1983 by the initiation of a supplemental instrumentation grant program. Replacement and upgrading of research equipment were identified as the most pressing priority needs for MBRS grantees in 1982 in order that the institutions be able to compete more successfully for other research support. The 20 supplemental grants ranging from $25,000 to $100,000 enabled MBRS grantees to obtain state-of-the-art instrumentation, including spectrophotometers, spectrometers, and ultra-centrifuges, plus other basic equipment items.

Data obtained during a short-term evaluation study of the MBRS Program suggest that grantee institutions are becoming more successful in obtaining other research and training grant support. There have been marked increases in NIH and PHS funding over two recent consecutive five-year periods of MBRS support (1973-1977 and 1978-1982, respectively), compared to the five years immediately preceding the inception of the program (1968-1972). For example, the percentage of current grantees receiving other support increased from 54 percent in the baseline period to 81 percent in the first five-year period (1973-1977) and to 94 percent in the most recent period (1978-1982). Non-MBRS dollar support increased from $126,000 baseline to $333,000 (1973-1977), and to $567,000 during the latest period (1978-1982).

FACULTY AND STUDENT DEVELOPMENT

Since 1972, the MBRS Program has graduated more than 6,000 minority students. They have entered graduate schools; medical, dental, and other health professional schools; and other health-related careers. In 1983, more than 1,200 students participated directly in research activities and attended scientific meetings and symposia. Many students made scientific presentations at these meetings, and some co-authored research publications.

Fiscal Year 1982 data, the most recent available, indicate that of the 533 MBRS graduates, 26 entered dental school, 167 entered medical school, 158 went to graduate school, and 97 continued their education at other health institutions. Most of the students who did not pursue advanced studies are employed in the health field. (See Figure II).

At 10 MBRS institutions, approximately 70 minority students received Ph.D. degrees while participating in MBRS-funded projects. They are currently engaged in biomedical research, either at the postdoctoral or faculty level.

Student participation at some institutions has been particularly active. For example, at Howard University, 169 MBRS-supported undergraduates, 179 graduate students, 13 dental students, and 31 medical students participated in biomedical research from 1972 to 1981. As of 1979, a total of 151 students had completed undergraduate degrees at this university, 14 had completed Ph.D. degrees, 21 had completed M.D.'s, and 27 had completed D.D.S. degrees.

MBRS faculty have continued to refine their research skills and increase their contributions to biomedical research. A total of 639 faculty members participated in 547 research projects in Fiscal Year 1983. As a result of MBRS Program faculty development efforts, 63 faculty investigators have won regular NIH grants, and 26 have been nominated to NIH advisory and review committees, compared to only 3 in 1973. Examples of research accomplishments by MBRS faculty in Fiscal Year 1983 follow.

A possible target for interferon action in the mammalian cell was recently discovered by researchers at New Mexico State University. They found that interferon rapidly inactivates the suspected target, an enzyme called ornithine decarboxylase (ODC), by phosphorylation. The inactivation of ODC by interferon seems to be especially significant because ODC activity is greatly stimulated by tumor-promoting agents and most hormones, and in the transformation of normal cells to cancer cells by certain viruses. The researchers believe that the enzyme induced by interferon to inhibit ODC by phosphorylation may be ODC kinase, an enzyme they recently discovered in the nucleus of the slime mold Physarum polycephalum and in rat liver cells. They are currently collaborating with an investigator at the Memorial Sloan-Kettering Institute for Cancer Research to determine whether ODC and the newly discovered enzyme indeed are involved in the action of interferon.

Short-term paralysis resulting from the interaction of marijuana with reserpine, a widely used antihypertensive drug, was observed recently in animal experiments conducted at the University of Texas at El Paso. Reserpine in large doses induces muscular rigidity and a state of motionlessness called akinesia. This effect in rats was increased more than 20-fold by delta-9-tetrahydrocannabinol (THC), one of many psychoactive compounds in marijuana. The enhancing effect of THC on reserpine-induced akinesia occurred within the first hour after oral administration and was not completely dissipated until about 11 hours later. The pronounced behavioral effect of THC on reserpine-induced akinesia may provide a key to measuring THC's action on other drugs that have important effects on nervous system function. The most important and direct application of the findings, however, may be the use of THC or a similar drug without psychoactive effects to increase the efficacy of reserpine in the treatment of hyperkinetic motor disorders.

At Bishop College, MBRS researchers are using a virus that attacks certain plants as a model of viral infection. They are studying brome mosaic virus (BMV) to understand more clearly how viral genes interact in causing disease and to apply this knowledge to viruses that attack higher organisms. The scientists selected BMV as the model because its replication and protein assembly processes involve only a few genes and because its genetic material is structurally similar to that of many medically important viruses. Like the viruses that cause influenza, polio, and rubella, BMV's genetic material is distributed among several molecules of RNA. Using a method called "RNA fingerprinting," the investigators analyzed gene fragments of the plant virus. They believe there may be a correlation between the unique poly(A) sequence in the RNA 3 molecule of BMV and the expression of the gene that codes for the coat protein, a gene present in both RNA 3 and 4. The coat protein surrounds

the nucleic acid of the virus, which invades host cells. It protects the nucleic acid until it reaches its target and participates in the infection of the cell.

In one MBRS-supported study at Atlanta University, the investigators found that dimethyl sulfoxide (DMSO), a chemical sometimes used by arthritis patients and athletes as a local remedy for aches and pains, caused significant chromosomal damage in Chinese hamster ovary cell cultures. DMSO, a by-product of paper manufacturing which is widely used as an industrial and laboratory solvent, is not approved by the U.S. Food and Drug Administration for use as a drug. When applied to the skin, it is quickly absorbed and circulates generally in the body tissues and fluids. The researchers found that DMSO concentrations of 1 to 4 percent increased chromosomal aberrations up to 21 percent, compared to 5 percent increased chromosomal aberrations for control cultures not exposed to DMSO. Other research has shown that DMSO caused a significant increase in chromosomal aberrations in the bone marrow cells of rats; high doses have produced congenital defects in chick embryos, rats, mice, and hamsters.

MEETINGS, WORKSHOPS, AND CONFERENCES

ANNUAL MBRS SYMPOSIUM

The 11th Annual MBRS Symposium was held in Washington, D.C., on April 7-9, 1983. Highlights included a keynote scientific lecture by NIH Director Dr. James Wyngaarden on inborn errors of purine metabolism, and a banquet address by Dr. Edward Brandt, Assistant Secretary for Health, on technology and medicine.

Five workshops were conducted in the following areas: selection of mini-computers for biomedical laboratories; cell culture technique and quality control; applications of monoclonal antibodies in biomedical research; recombinant DNA technology; and NMR studies in vivo. Seminars were held on sources of research funding; the status of animal welfare legislation; and the choice of career options between biomedical research, clinical medicine, or academic medicine.

Nine lectures were given by guest speakers on topics ranging from eukaryotic gene regulation to biomedical applications of artificial intelligence.

More than 700 scientific papers and posters were presented by MBRS students and faculty. Six awards of $500 each for research and presentation excellence were given to student scientists. The symposium was the largest gathering of minority biomedical researchers to date, with more than 2,000 attendees.

PROPHET WORKSHOPS

In anticipation of an upcoming PROPHET consortium, two workshops were conducted in December in Puerto Rico to educate MBRS and other appropriate

investigators on the uses of the PROPHET system. About 90 investigators and students attended the workshops, including representatives from the 4 campuses of the University of Puerto Rico, Inter-American University, Catholic University of Puerto Rico, the San Juan office of the Center for Disease Control, the San Juan Veterans' Hospital, and the Cancer Center at the University of Puerto Rico Medical School.

MBRS PROGRAM DIRECTORS MEETING

The MBRS program directors met January 6-8, 1983, in Washington, D.C. A wide range of program and policy issues were discussed, including common problems encountered during review, advantages and disadvantages of different review mechanisms, levels of funding and funding priorities, and changes in fiscal policy. The directors commented on draft guidelines for associate investigators and for the new initiative for instrumentation grants. Recommendations were made to increase funds for student salaries (particularly for undergraduates) and for travel. Small group discussions also were held with Triton, Inc., personnel who are involved in a short-term evaluation of the MBRS Program.

NARRC/MBRS WORK GROUP RETREAT

The Council MBRS Work Group, together with several General Research Support Review Committee members, program directors, and other representatives of the minority research community, met September 12-13, 1983, in Washington, D.C., to review program goals, discuss policy and program management issues, and develop recommendations for future directions for the MBRS Program. There was general agreement on program goals, with retreat participants recommending that a number of new initiatives and new funding mechanisms be developed to meet the diverse needs of MBRS-eligible institutions, and that application guidelines, review criteria, and reporting requirements be improved.

SHORT-TERM MBRS PROGRAM EVALUATION

The contract with Triton, Inc., for a short-term evaluation of the program, which began in September 1982, is nearing completion. Three interim reports were submitted on: 1) the evaluation team's understanding of the program, 2) an assessment of what aspects should be addressed in a short-term evaluation, and 3) a proposed data collection strategy. The team interviewed approximately 300 persons; reviewed program documentation, external literature, and grantee files; and conducted 13 field visits during the course of the study. A draft final report was submitted in September 1983, incorporating the team's findings and making recommendations for measuring and improving program effectiveness.

ORGANIZATIONAL CHANGES

A major change in internal DRR organization connected with MBRS activities took place in January 1983. To be consistent with the NIH tradition of separating peer review decisions from program funding and management

considerations, all MBRS peer review functions have been moved out of the program branch. An executive secretary position was established to be responsible for review of MBRS applications, under the DRR Office for Review. The program chief and staff continue to be involved full-time in program development, policy formulation, and all other program management activities.

POLICY CHANGES

Policy changes implemented during the year included the development of new guidelines and review criteria for associate investigators, the limitation of faculty summer salary support to a maximum of 2 months, and the increase of undergraduate student salary support from $3,000 to $3,600 per year. Applicants for competing renewal of an MBRS Program may request support for four years instead of three (a policy adopted in 1982); the first grant awards reflecting four-year approvals were made this year.

Interim policies adopted in June 1983 require pre-submission peer review of MBRS subprojects by applicant institutions, limit the total number of subprojects to 25 or fewer, and limit the total dollar amount requested in an application to $2 million per year and grant awards to $1.5 million per year, including indirect costs.

FUTURE DIRECTIONS

The current DRR Five-Year Plan outlines needs and opportunities and specifies goals and planned activities for the MBRS Program in the mid-1980s. The major goals are:

- To expand activities that enhance institutional biomedical research capability in institutions that show need and promise
- To promote collaborative initiatives with the MARC Program, with other NIH programs, and with other agencies
- To expand research career enrichment opportunities for faculty
- To continue to encourage and motivate students to choose biomedical research careers.

The program intends to maintain a level of 70 or more fully funded MBRS programs.

OTHER PLANNED ACTIVITIES

INSTRUMENTATION AWARDS

The need for instrumentation continues to be of high priority. MBRS institutions have developed research programs which require the acquisition of

sophisticated new instrumentation that can be shared, and the replacement of obsolete existing equipment. The quality and capability of instrumentation will be factors in the effectiveness and productivity of MBRS researchers. Because instrumentation can enhance institutional research capability, this initiative was implemented in 1983 and will be continued. Up to $1 million has been designated for instrumentation in 1984.

The Advisory Committee and Council have identified four areas of high priority that require specific action to carry out program goals. The areas are listed below in order of importance.

FACULTY RESEARCH CAREER ENRICHMENT AWARDS

Many faculty at MBRS institutions have not been able to compete successfully for external research funds. Consequently, biomedical research activities have been confined to those elements which are supported through direct MBRS support. The amount of biomedical research carried out at these institutions can be significantly increased by making investigators more competitive in other public and private funding areas.

The Advisory Committee and Council propose to expand research career development of faculty at MBRS-supported institutions by awarding Research Career Enrichment Awards to faculty. These awards would give faculty off-campus research experiences at research-intensive laboratories for a period of up to one year and would permit faculty to collaborate with scientists at host laboratories.

SEED MONEY FOR NEW AND RETURNING FULL-TIME TEACHING FACULTY

Faculty with full-time teaching responsibilities at MBRS-supported institutions are in need of start-up funds to conduct preliminary studies to develop more competitive grant proposals for MBRS or other health-related research programs.

Many new or returning faculty members at MBRS institutions have been well-trained and have a strong interest in research, but are unable to obtain even modest resources to develop a strong proposal. Many of these institutions are financially hard-pressed and unable to meet this need, which is recognized as important for the professional growth of their faculty. Eligibility requirements for Biomedical Research Support Grants have made it difficult for the majority of MBRS grantees to qualify for this traditional NIH source of seed money.

BIOMEDICAL RESEARCH FACILITIES IMPROVEMENT

As the research capabilities of MBRS institutions expand and more animal research is employed, the need for more adequate animal facilities arises. Special requirements for feeding, handling, caging, ventilation, and meeting other laboratory environmental conditions are continually arising. In addi-

tion, renovations of laboratory facilities are essential to the expanding research capabilities at MBRS institutions.

PORTABLE FELLOWSHIPS FOR FORMER MBRS STUDENTS WITH BACCALAUREATE DEGREES

Many MBRS undergraduates are unable to obtain support to continue their research interests after graduation because of: 1) lack of graduate programs at their undergraduate institutions, 2) limited research opportunities at their institutions, 3) stiff competition for available funds at major research schools, 4) inability to match research interests with laboratories that have graduate student support available, and 5) little opportunity for support in health professions schools. Only one-third of MBRS students receiving bachelor's degrees each year go on to graduate school.

Portable fellowships would provide much more flexibility in selecting a research area and more choices of institutional affiliation for those who go to graduate school; the opportunity for those in health professions schools to maintain an interest in research and to work toward a clinical research career; and, for those who elect to discontinue advanced studies and work instead, expanded opportunities to obtain graduate research training. All of these efforts are important to achieve the MBRS goal of increasing the number and quality of minority biomedical scientists.

ADDITIONAL FIVE-YEAR PLAN ACTIVITIES

Student Initiatives

In many MBRS institutions, little opportunity exists for students to interact with researchers other than their mentors. Other factors that motivate students for biomedical research careers may be lacking because many MBRS institutions are isolated and small. Our limited experience in sending MBRS students off-campus during summers to NIH laboratories and other major universities has demonstrated that this is a most rewarding investment. To provide MBRS students with more opportunity for research exposure, summer research experiences are proposed. Salaries, as well as travel support, would be provided for students to spend a summer at a laboratory in a major research setting.

Over the years, the MBRS Program has graduated 1,500-2,000 students who have entered professional schools of medicine, dentistry, veterinary medicine, and other health professions. Many of these students continue their interest in research but find it difficult to obtain research support. The program hopes to provide support for these students, on a pilot basis, to engage in research during their "off" quarters or summers. Eligibility would be based on previous MBRS participation. Payments would be made by the MBRS home institution.

Collaborative Activities

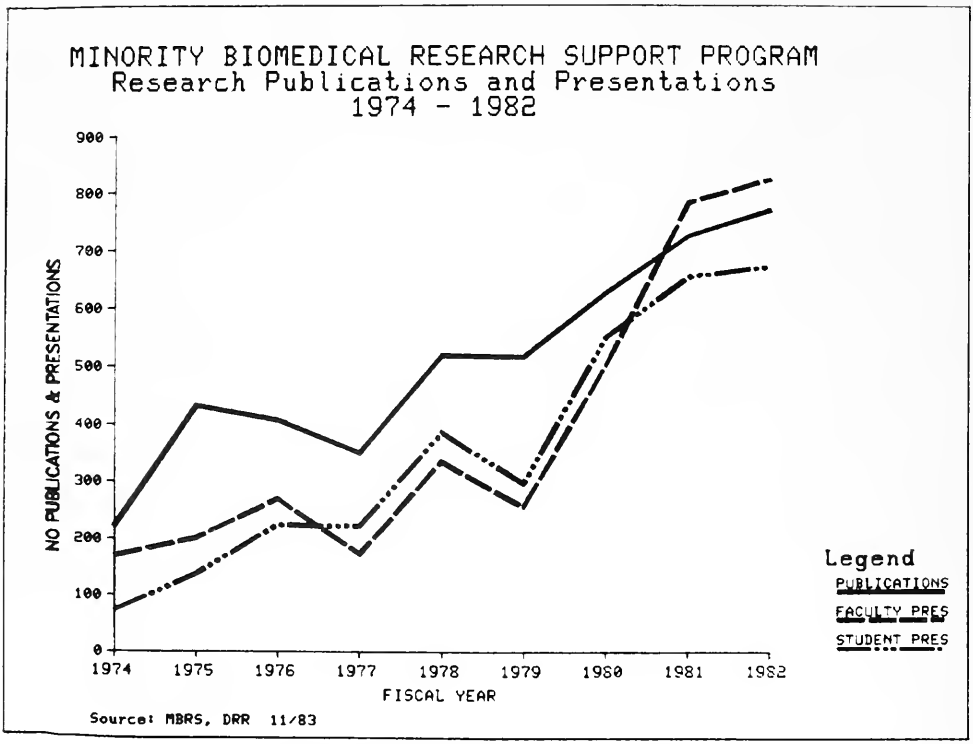
The planning for collaborative efforts is geared to:

- Provide for established scientists at major institutions to visit MBRS schools on a long-term basis in collaboration with the Minority Access to Research Careers (MARC) Program of the National Institute of General Medical Sciences
- Provide for co-funding of training activities, also possibly in collaboration with the MARC Program
- Increase collaboration with the private sector. The MBRS Symposium might be used as a mechanism to initiate interaction between pharmaceutical, chemical, and other companies and MBRS investigators
- Develop collaborative partnership between the MBRS Program and the local community.

COUNCIL MBRS WORK GROUP RETREAT RECOMMENDATIONS

The work group addressed needs for improving and developing the MBRS Program and made a number of recommendations to the Council which, if adopted, will significantly increase program flexibility in the future. Examples of new initiatives proposed by this group are: 1) a program to provide motivational experiences and exposure to biomedical research for minority students at two-year colleges, 2) a "research initiation" program which would provide basic institutional support for initiation of biomedical research activities at small four-year colleges, and 3) development of a "thematic" approach, whereby large MBRS institutions could submit multiple, small applications directed toward specific research areas or themes. These types of initiatives might well be part of MBRS activities in the next few years.

Figure I

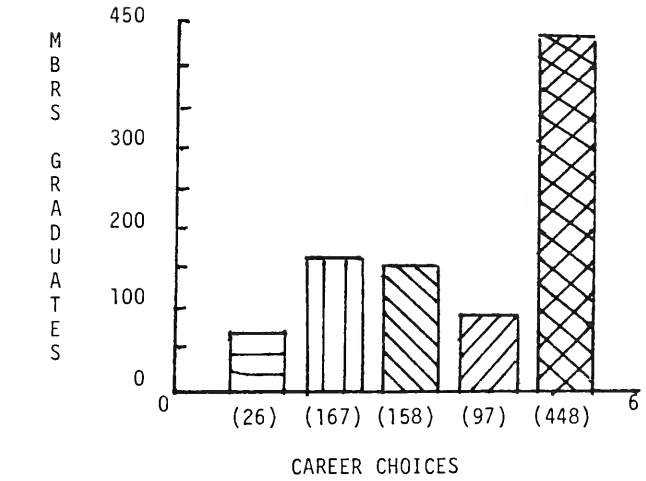


NO. OF GRANTEES AND NO. OF PROJECTS
FOR WHICH DATA ARE REPORTED EACH YEAR

0 YEAR	1 NO. OF PROJECTS	2 NO. OF GRANTEES
1. 1974	314	63
2. 1975	408	69
3. 1976	378	75
4. 1977	257	74
5. 1978	318	71
6. 1979	380	71
7. 1980	488	79
8. 1981	486	79
9. 1982	521	78
10. 1983	547	79

Figure II

CAREER CHOICES OF THE 1982 MBRS GRADUATES



Dental School
Medical School
Graduate School
Other Health Related Schools
Total

Office of Grants and Contracts Management
Division of Research Resources

The Office of Grants and Contracts Management (OGCM) staff played an important role in the review, negotiation, award-making, and administration of the DRR grant programs. The OGCM also aided in the administration of research and development contracts made by the Research Contracts Branch, Division of Contracts and Grants.

During Fiscal Year 1983, a total of $217,411,000 was awarded: 1,304 grant awards were made in the amount of $213,138,000, and 15 contracts were entered into in the amount of $4,273,000. In Fiscal Year 1983, the total number of DRR awards increased by 12.2 percent over Fiscal Year 1982, and the dollar amount awarded increased by 16.4 percent.

During Fiscal Year 1983, $9,899,000, or 4.6 percent of the total amount awarded by DRR, came from other NIH institutes for co-funding the Minority Biomedical Research Support (MBRS) grant program. There was more than a $1 million or 15.1 percent increase in the co-funding of MBRS grants compared to Fiscal Year 1982.

The tables and figures that follow reflect the total DRR grant and R&D contract efforts for Fiscal Year 1983.

Table I

DIVISION OF RESEARCH RESOURCES

FY 1983 OVERVIEW OF EXTRAMURAL GRANTS AND R&D CONTRACT ACTIVITIES

Program	Funding	Major Resources Supported
General Clinical Research Centers Program	$ 74,584,000	• 74 clinical research centers • More than 3,400 research projects • 34 Clinical Associate Physicians • 22 CLINFO sites
Biotechnology Resources Program	$ 25,382,000	• 81 biotechnology resources 21 knowledge engineering and information technology in biomedicine 15 biomedical engineering and digital technology 45 technologies for study of biomolecular and cellular structures and function
Animal Resources Program	$ 28,316,000	• 7 primate centers, including more than 475 research projects at centers • 5 primate breeding projects • 52 animal research and resource projects • 13 training programs
Biomedical Research Support Program	$ 58,893,000	• Biomedical Research Support Grants to 530 institutions that supported more than 9,000 pilot and regular research projects • Shared instrumentation awards to 91 institutions • 666 students through Minority High School Research Apprenticeship Program
Minority Biomedical Research Support Program	$ 27,767,000	• 80 institutions (4 received no FY 83 funds) • 547 research projects • 639 faculty, 894 undergraduate, and 340 graduate
Office of the Director	$ 1,469,000	Contracts for: • culture collection • workshop models for biomedical research • Research Resources Reporter • program evaluation
Total	$217,411,000 1/	

1/ Includes $9,899,000 of non-DRR-appropriated funds. See footnotes on Table II for details.

OGCM FY-1983

Table II

DRR FY 1983 GRANT AND R&D CONTRACT AWARDS BY MECHANISM

(Dollars in Thousands)

PROGRAM ACTIVITY	Research Grants									Training Programs			Contracts (R&D Contracts, Inter/ Intra-Agency Agreements)		
	Research Centers			Other Research											
	Type	No.	Amount	Type	No.	Amount				Type	No.	Amount	Type	No.	Amount
General Clinical Research Centers Program.....		M01s			P09s										
	2	17	$16,298	3	(1)	$ 200							Cont. Mod.	1	$ 53
	3	19	1,278		R24s										
	5	57	55,635	2	1	$ 58									
	7	1	898		R43s										
		94	$74,109 1/	1	2	$ 64									
					S06s										
				5	(1)	$ 100									
Biotechnology Resources Program.....		P41s			P09s										
	1	9	$ 4,559	3	1	$ 15							Cont. Mod.	3	$1,685 2/
	2	4	1,769		R01s										
	3	5	844	3	(1)	$ 10							Intra-Agency	2	160
	5	33	13,031		R03s									5	$1,845
		51	$20,203	1	14	$ 298									
					R13s										
				1	1	$ 15									
					R23s										
				1	1	$ 51									
					R24s										
				1	3	$ 720 3/									
				3	1	18									
				5	5	2,032									
					9	$2,770									
					R43s										
				1	3	$ 175									

Table II
DRR FY 1983 GRANT AND R&D CONTRACT AWARDS BY MECHANISM (CONTD)
(Dollars in Thousands)

	Research Grants									Contracts (R&D Contracts, Inter/ Intra-Agency Agreements)		
	Research Centers			Other Research			Training Programs					
	Type	No.	Amount	Type	No.	Amount	Type	No.	Amount	Type	No.	Amount
Animal Resources Program.....		P40s			K01s			F32s				
	1	3	$ 305	1	4	$ 184	1	1	$ 21	Cont.		
	2	5	822		P09s		5	2	42	Mod.	2	$ 336 4/
	3	1	15	3	(1)	$ 95		3	$ 63	Intra-		
	5	27	4,748		R13s			T32s		Agency	1	500
		36	$ 5,890	1	1	$ 18 5/	2	2	162		3	$ 836
		P51s			R23s		5	7	470			
	2	2	$ 5,153	1	1	$ 62		9	$ 632			
	5	5	14,466	5	1	36		T35s				
		7	$19,619 6/		2	$ 98	5	1	$ 13			
					R24s							
				1	3	$ 249						
				2	1	30						
				3	1	139						
				5	5	403						
					10	$ 821						
					R43s							
				1	1	$ 47						
Biomedical Research Support Program.....					S03s							
				1	29	$ 113						
				2	248	886						
					277	$ 999						
					S07s							
				1	28	$ 550						
				2	501	44,323						
				3	1	21						
					530	$44,894						
					S10s							
				1	91	$14,000						

Table II
DRR FY 1983 GRANT AND R&D CONTRACT AWARDS BY MECHANISM (CONTD)
(Dollars in Thousands)

PROGRAM ACTIVITY	Research Grants: Research Centers Type	No.	Amount	Research Grants: Other Research Type	No.	Amount	Training Programs Type	No.	Amount	Contracts (R&D Contracts, Inter/Intra-Agency Agreements) Type	No.	Amount
Minority Biomedical Research Support Program...				P09s 3	(1)	$ 175				Cont. Mod.	(1)	$ 70
				R13s 5	1	$ 81						
				S06s 1	5	$ 718						
				2	30	13,527						
				3	83	2,696						
				5	36	10,500						
					154	$27,441 7/						
Office of the Director.....										Cont. New	2	$ 265
										Cont. Mod.	4	1,204
											6	$1,469 8/
DIVISION TOTALS		188	$119,821		1103	$92,609		13	$ 708		15	$4,273

1/ Includes $ 14,000 non-DRR-appropriated funds (intra-agency agreement)
2/ Includes $ 915,000 non-DRR-appropriated funds ($825,000 co-funding, $90,000 inter/intra-agency agreements)
3/ Includes $ 62,000 non-DRR-appropriated funds (co-funding)
4/ Includes $ 86,000 non-DRR-appropriated funds (co-funding)
5/ Includes $ 8,000 non-DRR-appropriated funds (co-funding)
6/ Includes $ 207,000 non-DRR-appropriated funds (intra-agency agreement)
7/ Includes $7,693,000 non-DRR-appropriated funds ($6,343,000 co-funding, $1,350,000 intra-agency agreement)
8/ Includes 914,000 non-DRR-appropriated funds (co-funding)
TOTAL $9,899,000

Table III

DIVISION OF RESEARCH RESOURCES

FY 83 AWARDS BY COMPONENT
Research Grants, Research Training, and
R&D Contracts

General Clinical Research Centers Program	Research Centers	$ 74,109,000	
	Other Research	422,000	
	Contracts	53,000	
		$ 74,584,000	(34.3%)
Biotechnology Resources Program	Research Centers	$ 20,203,000	
	Other Research	3,334,000	
	Contracts	1,845,000	
		$25,382,000	(11.7%)
Animal Resources Program	Research Centers	$ 25,509,000 1/	
	Other Research	1,263,000	
	Training	708,000	
	Contracts	836,000	
		$ 28,316,000	(13.0%)
Biomedical Research Support Program	Other Research	$ 59,893,000	(27.5%)
Minority Biomedical Research Support Program	Other Research	$ 27,697,000	(12.8%)
	Contracts	70,000	
		$ 27,767,000	
Office of the Director	Contracts	$ 1,469,000	(0.7%)
		$217,411,000 2/	(100%)

1/ $19,619,000 of this amount was for Primate Centers
2/ Includes $9,899,000 of non-DRR-appropriated funds. See footnotes on Table II for details.

OGCM FY-1983

Figure I

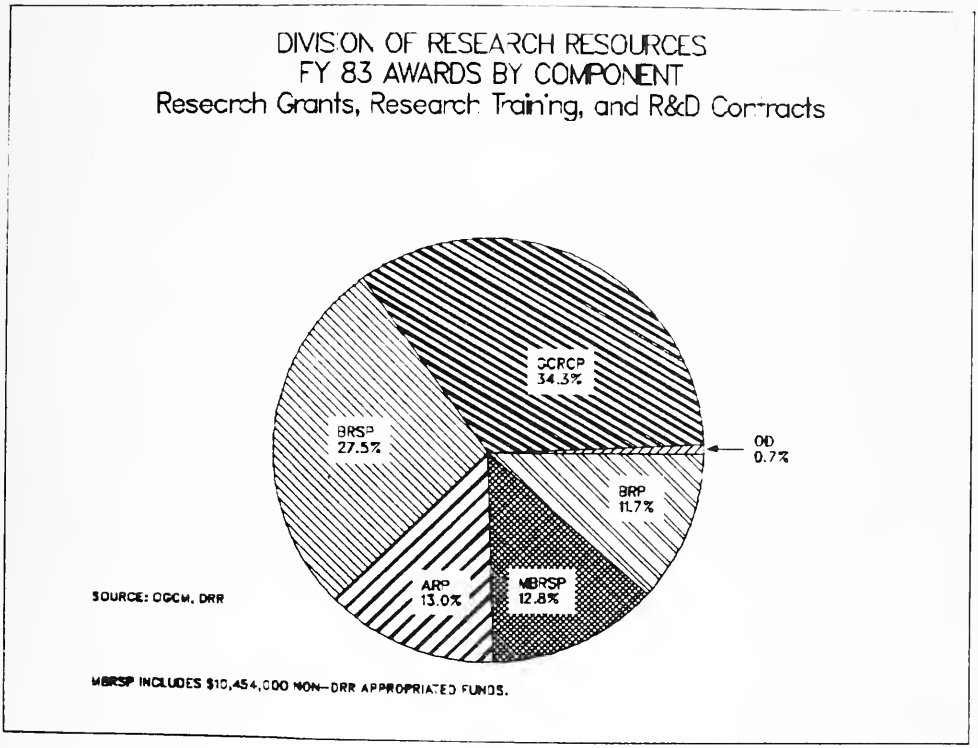

DIVISION OF RESEARCH RESOURCES
FY 83 AWARDS BY COMPONENT
Research Grants, Research Training, and R&D Contracts
DCRCP
34.3%
OD
0.7%
BRP
11.7%
MBRSP
12.8%
ARP
13.0%
BRSP
27.5%
SOURCE: OGCM, DRR
MBRSP INCLUDES $10,454,000 NON-DRR APPROPRIATED FUNDS.

Figure II

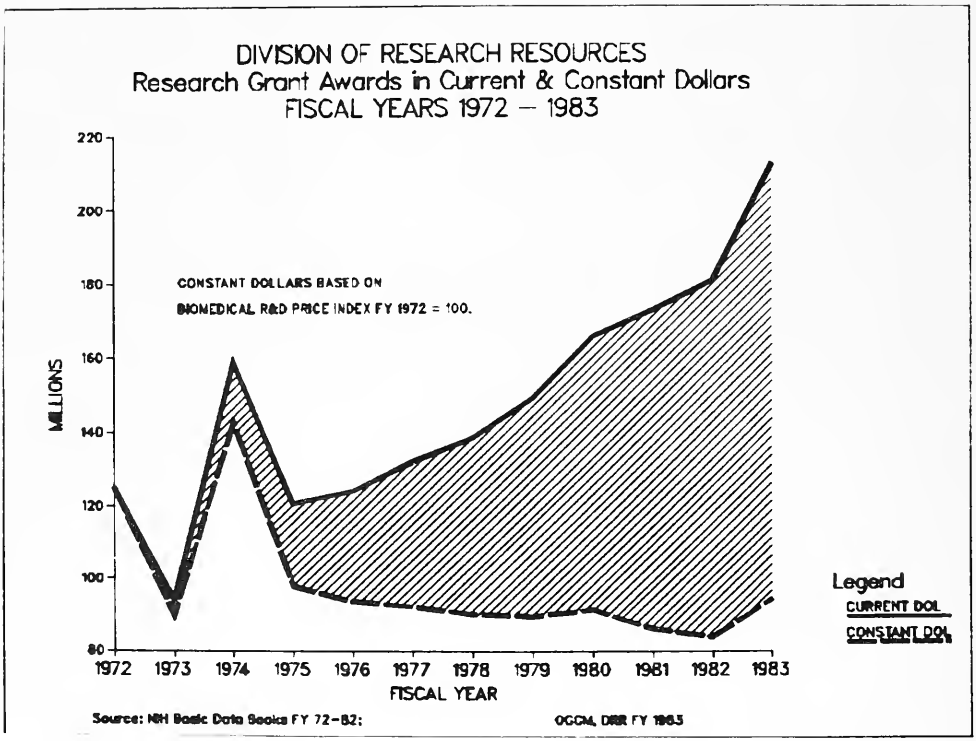

DIVISION OF RESEARCH RESOURCES
Research Grant Awards in Current & Constant Dollars
FISCAL YEARS 1972 – 1983
CONSTANT DOLLARS BASED ON
BIOMEDICAL R&D PRICE INDEX FY 1972 = 100.
MILLIONS
220
200
180
160
140
120
100
80
1972
1973
1974
1975
1976
1977
1978
1979
1980
1981
1982
1983
FISCAL YEAR
Legend
CURRENT DOL
CONSTANT DOL
Source: NIH Basic Data Books FY 72-82;
OGCM, DRR FY 1983

Figure III

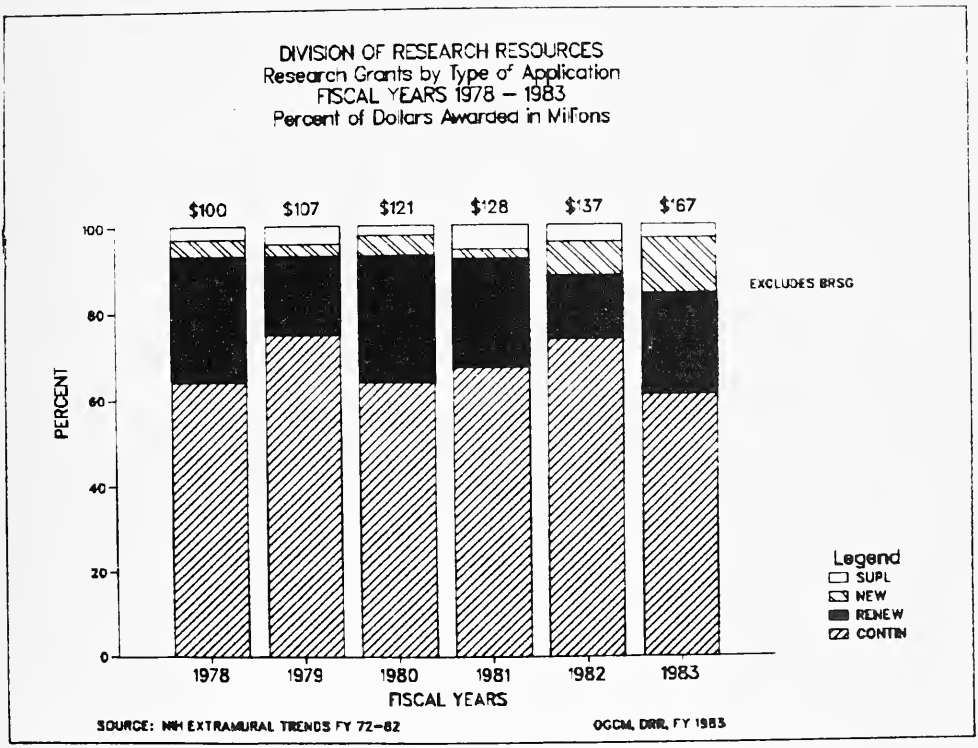
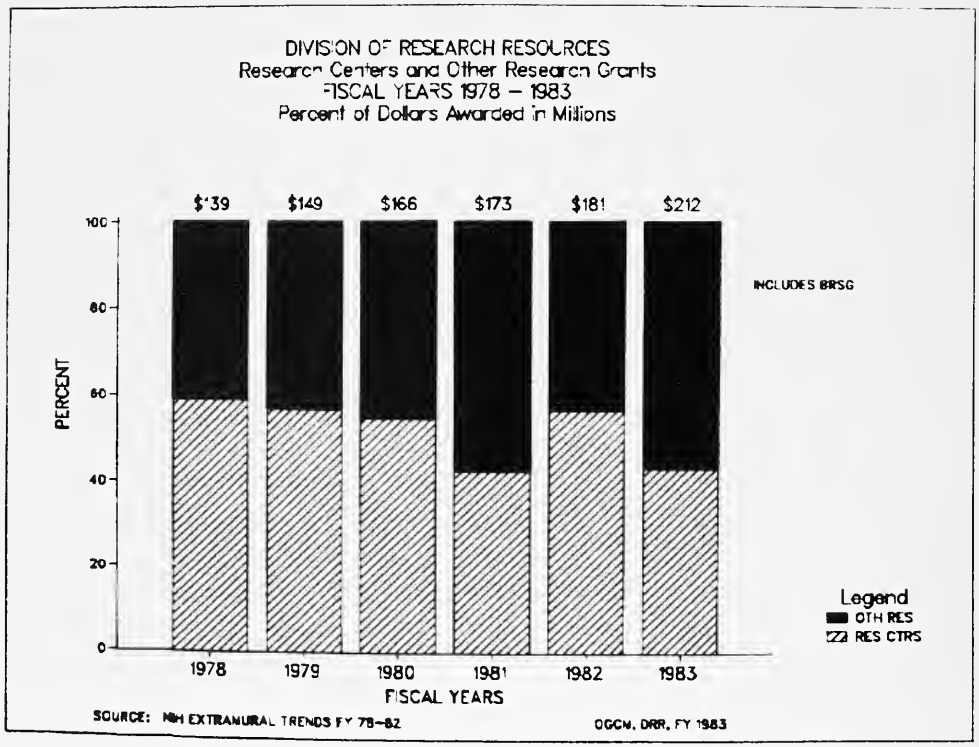

DIVISION OF RESEARCH RESOURCES
Research Grants by Type of Application
FISCAL YEARS 1978 – 1983
Percent of Dollars Awarded in Millions
$100
$107
$121
$128
$137
$167
EXCLUDES BRSG
PERCENT
100
80
60
40
20
0
1978
1979
1980
1981
1982
1983
FISCAL YEARS
Legend
SUPL
NEW
RENEW
CONTIN
SOURCE: NIH EXTRAMURAL TRENDS FY 72-82
OCCM, DRR, FY 1983

Figure IV



* U.S. GOVERNMENT PRINTING OFFICE: 1983-421-132:3287